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I, JONNE YABSLEY, ACTING TEAM LEADER EXAMINATION SUPPORT & SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. PQ 9552 for a patent by FUJISAWA PHARMACEUTICAL CO., LTD. filed on 21 August 2000.

WITNESS my hand this
Twentieth day of February 2001

J R Yabsley

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Regulation 3.2

Fujisawa Pharmaceutical Co., Ltd.

AUSTRALIA

Patents Act 1990

PROVISIONAL SPECIFICATION

for the invention entitled:

"New Compound"

The invention is described in the following statement:

DESCRIPTION

NEW COMPOUND

TECHNICAL FIELD

The present invention relates to new polypeptide compounds and salts thereof which are useful as a medicament.

BACKGROUND ART

In U.S. Pat. No. 5,376,634, 5,569,646, WO 96/11210 and WO 99/40108, there are disclosed the polypeptide compound and a pharmaceutically acceptable salt thereof, which have antimicrobial activities (especially antifungal activity).

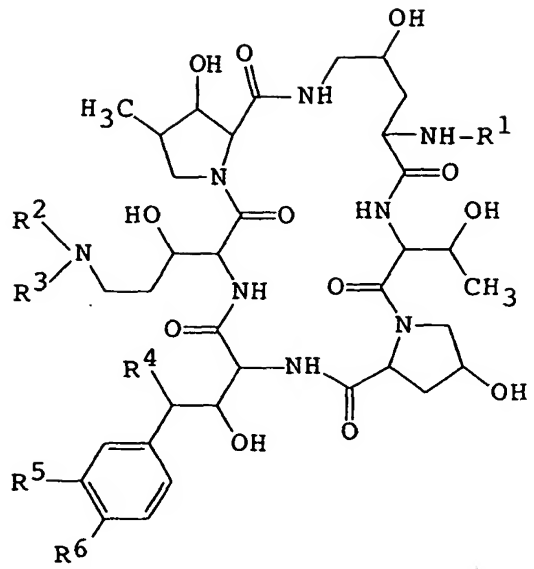
DISCLOSURE OF INVENTION

The present invention relates to new polypeptide compound and a salt thereof.

More particularly, it relates to new polypeptide compound and a salt thereof, which have antimicrobial activities [especially, antifungal activities, in which the fungi may include Aspergillus, Cryptococcus, Candida, Mucor, Actinomyces, Histoplasma, Dermatophyte, Malassezia, Fusarium and the like.], inhibitory activity on β-1,3-glucan synthase, and further which are expected to be useful for the prophylactic and/or therapeutic treatment of Pneumocystis carinii infection (e.g. Pneumocystis carinii pneumonia) in a human being or an animal, to a process for preparation thereof, to a pharmaceutical composition comprising the same, and to a methods for the prophylactic and/or therapeutic treatment of infectious disease including Pneumocystis carinii infection (e.g. Pneumocystis carinii pneumonia) in a human being or an animal.

The object polypeptide compounds of the present invention are new and can be represented by the following general formula (I):

general formula (I):



(I)

wherein

R^1 is hydrogen or acyl group,

R^2 is hydrogen or acyl group,

R^3 is lower alkyl which has one or more hydroxy or protected hydroxy,

R^4 is hydrogen or hydroxy,

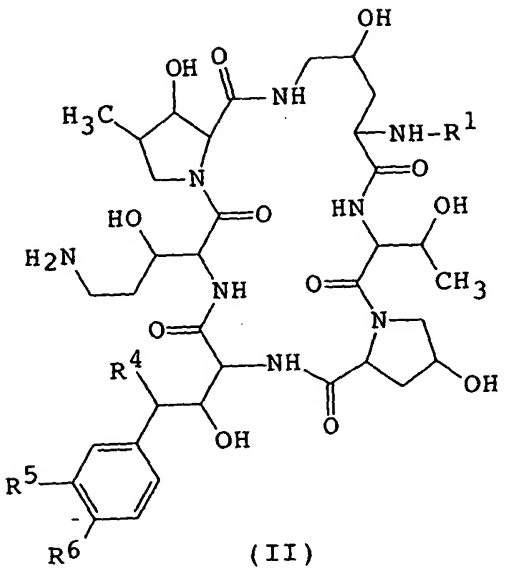
R^5 is hydrogen, hydroxy, lower alkoxy or hydroxysulfonyloxy, and

R^6 is hydroxy or acyloxy,

or a salt thereof.

The new polypeptide compound (I) or a salt thereof can be prepared by the process as illustrated in the following reaction schemes.

Process 1

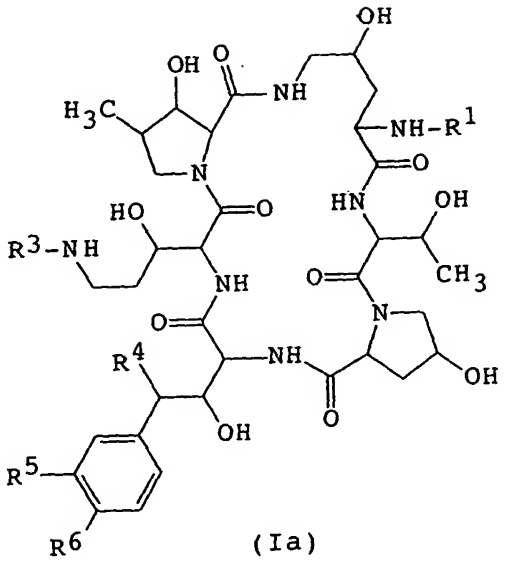


(II)

or its reactive derivative at the amino group or a salt thereof

R^3=O (III)

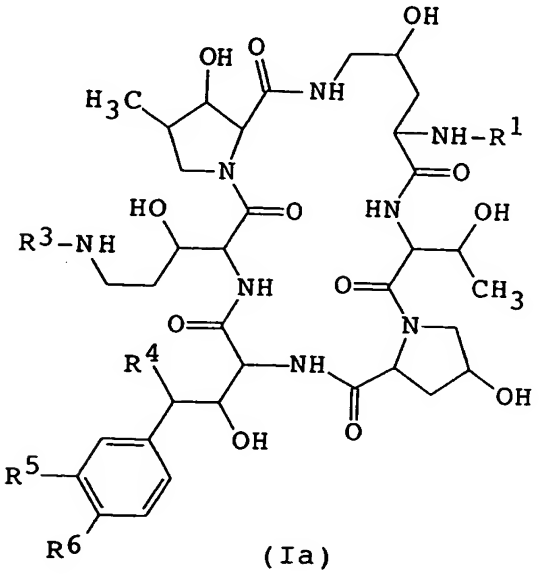
or its reactive derivative or a salt thereof



(Ia)

or a salt thereof

Process 2

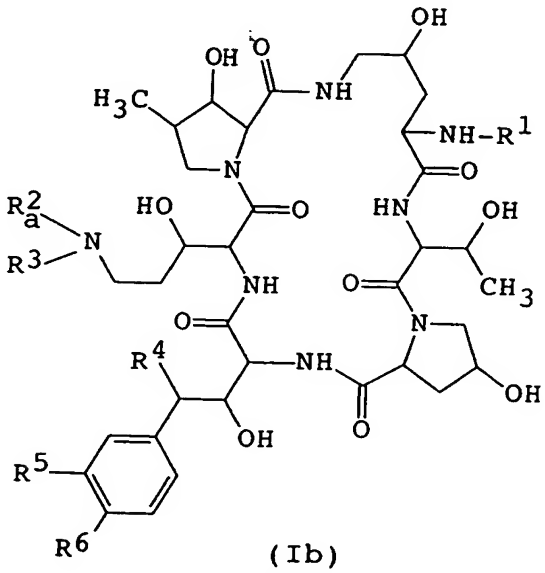


(Ia)

or its reactive derivative at the amino group or a salt thereof

R_a^2-OH (IV)

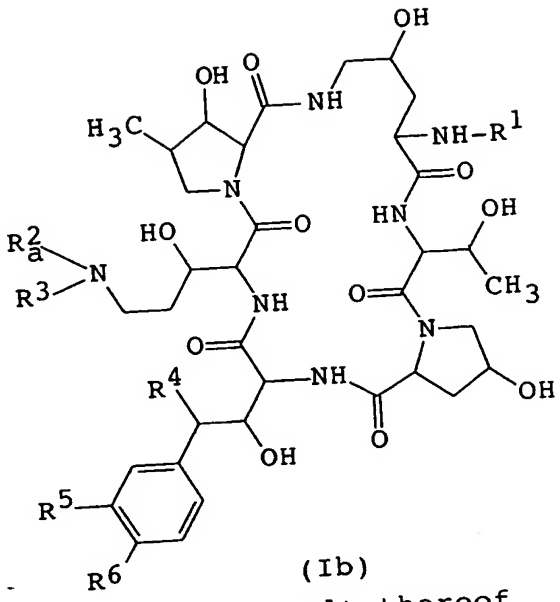
or its reactive derivative at the carboxy group or a salt thereof



(Ib)

or a salt thereof

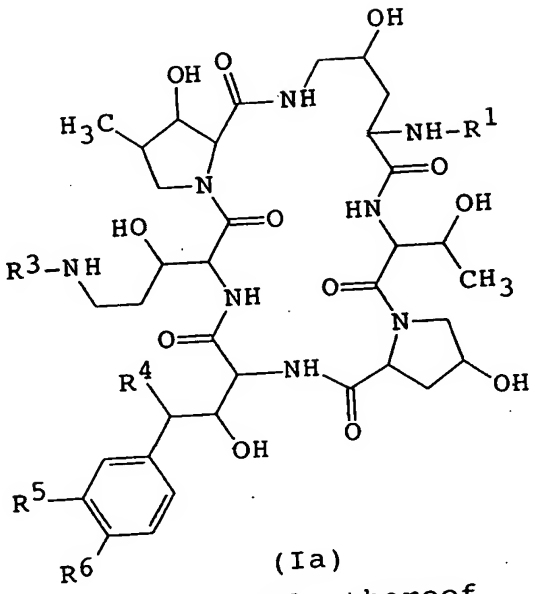
Process 3



(Ib)

or a salt thereof

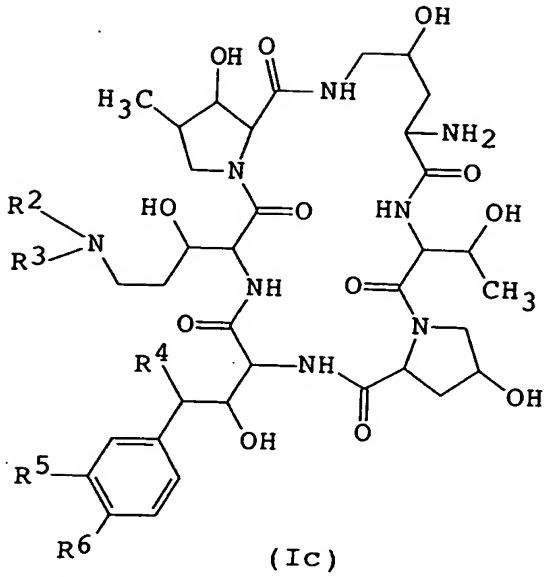
elimination reaction



(Ia)

or a salt thereof

Process 4

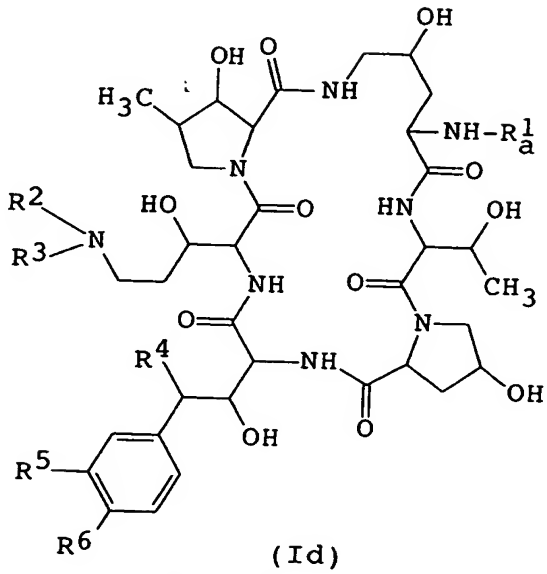


(Ic)

or its reactive derivative at the amino group or a salt thereof

R_a^1-OH (V)

or its reactive derivative at the carboxy group or a salt thereof



(Id)

or a salt thereof

wherein R^1, R^2, R^3, R^4, R^5 and R^6 are defined above,
R^1_a is acyl group, and
R^2_a is acyl group.

Suitable salt of the new polypeptide compound (I) is a pharmaceutically acceptable and conventional non-toxic salt, and may include a salt with a base or an acid addition salt such as a salt with an inorganic base, for example, an alkali metal salt (e.g., sodium salt, potassium salt, etc.), an alkaline earth metal salt (e.g., calcium salt, magnesium salt, etc.), an ammonium salt;
a salt with an organic base, for example, an organic amine salt (e.g., triethylamine salt, diisopropylethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, 4-dimethylaminopyridine salt, etc.);
an inorganic acid addition salt (e.g., hydrochloride hydrobromide, sulfate, phosphate, etc.);
an organic carboxylic sulfonic acid addition salt (e.g., formate, acetate, trifluoroacetate, maleate, tartrate, fumarate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.);
a salt with a basic or acidic amino acid (e.g., arginine, aspartic acid, glutamic acid, etc.).

Suitable examples and illustration of the various definitions in the above and subsequent descriptions of the present specification, which the present invention intends to include within the scope thereof, are explained in detail as follows:

The term "lower" is used to intend a group having 1 to 6 carbon atom(s), unless otherwise provided.

Suitable example of "one or more" may be the number of 1 to 6, in which the preferred one may be the number of 1 to 3, and

the most preferred one may be the number of 1 or 2.

Suitable example of "halogen" may be fluorine, chlorine, bromine, iodine and the like.

Suitable example of "lower alkoxy" may include straight or branched one such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, tert-pentyloxy, neo-pentyloxy, hexyloxy, isohexyloxy and the like.

Suitable example of "higher alkoxy" may include straight or branched one such as heptyloxy, octyloxy, 3,5-dimethyloctyloxy, 3,7-dimethyloctyloxy, nonyloxy, decyloxy, undecyloxy, dodecyloxy, tridecyloxy, tetradecyloxy, hexadecyloxy, heptadecyloxy, octadecyloxy, nonadecyloxy, icosyloxy, and the like.

Suitable example of "lower alkyl" may include straight or branched one having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, tert-pentyl, neo-pentyl, hexyl, isohexyl and the like.

Suitable example of "higher alkyl" may include straight or branched one such as heptyl, octyl, 3,5-dimethyloctyl, 3,7-dimethyloctyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, icosyl, and the like.

Suitable example of "aryl" and "ar" moiety may include phenyl which may have lower alkyl (e.g., phenyl, mesityl, xylyl, tolyl, etc.), naphthyl, anthryl, indanyl, fluorenyl, and the like, and this "aryl" and "ar" moiety may have one or more halogen.

Suitable example of "aroyl" may include benzoyl, toluoyl, naphthoyl, anthrylcarbonyl, and the like.

Suitable example of "heterocyclic group" may include unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, dihydropyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g.

1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolidinyl, imidazolidinyl, piperidyl, piperazinyl, azetidinyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s), for example, indolyl, isoindolyl, indolinyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.), etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholinyl, sydnonyl, morpholino, etc.;

unsaturated condensed heterocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, isothiazolyl, thiadiazolyl (e.g., 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.), dihydrothiazinyl, etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example thiazolidinyl, thiomorpholinyl, thiomorpholino, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 sulfur atom(s), for example, thienyl, dihydrodithiinyl, dihydrodithionyl, etc.;

unsaturated condensed heterocyclic group containing 1 or 2

sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, imidazothiadiazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom, for example, furyl etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 oxygen atom(s), for example, tetrahydrofuran, tetrahydropyran, dioxacyclopentane, dioxacyclohexane, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom and 1 or 2 sulfur atom(s), for example, dihydrooxathiinyl, etc.;

unsaturated condensed heterocyclic group containing 1 or 2 sulfur atom(s), for example benzothienyl, benzodithiinyl, etc.;

unsaturated condensed heterocyclic group containing an oxygen atom and 1 or 2 sulfur atom(s), for example, benzoxathiinyl, etc.; and the like, and this "heterocyclic group" may have one or more suitable substituent(s) selected from the group consisting of lower alkyl, oxo, cyclo(lower)alkyl, hydroxy(lower)alkyl, carboxy(lower)alkanoyl which may have amino and heterocycliccarbonyl.

Suitable example of "cyclo(lower)alkyl" may include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like, and this "cyclo(lower)alkyl" may have one or more lower alkyl.

Suitable example of "cyclo(lower)alkyloxy" may include cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, and the like.

Suitable example of "acyl group" may include aliphatic acyl, aromatic acyl, arylaliphatic acyl and heterocyclic-aliphatic acyl derived from carboxylic acid, carbonic acid, carbamic acid, sulfonic acid, and the like.

Suitable example of said "acyl group" may be illustrated as follows.

Carboxy; carbamoyl; mono or di(lower)alkylcarbamoyl (e.g., methylcarbamoyl, dimethylcarbamoyl, ethylcarbamoyl, diethylcarbamoyl, etc.)

Aliphatic acyl such as lower or higher alkanoyl (e.g., formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, dodecanoyl, tridecanoyl, tetradecanoyl, pentadecanoyl, hexadecanoyl, heptadecanoyl, octadecanoyl, nonadecanoyl, icosanoyl, etc.);
lower or higher alkoxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl, t-pentyloxycarbonyl, heptyloxycarbonyl, etc.); lower alkenyloxycarbonyl (e.g., vinyloxycarbonyl, propenyloxycarbonyl, allyloxycarbonyl, butenyloxycarbonyl, butedienyloxycarbonyl, pentenyloxycarbonyl, hexenyloxycarbonyl, etc.);
lower or higher alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl, etc.);
lower or higher alkoxysulfonyl (e.g., methoxysulfonyl, ethoxysulfonyl, etc.); or the like;

Aromatic acyl such as
aroyl (e.g., benzoyl, toluoyl, naphthoyl, etc.);
ar(lower)alkanoyl [e.g., phenyl(C_1-C_6)alkanoyl (e.g., phenylacetyl, phenylpropanoyl, phenylbutanoyl, phenylisobutanoyl, phenylpentanoyl, phenylhexanoyl, etc.), naphthyl(C_1-C_6)alkanoyl (e.g., naphthylacetyl, naphthylpropanoyl, naphthylbutanoyl, etc.), etc.];
ar(lower)alkenoyl [e.g., phenyl(C_3-C_6)alkenoyl (e.g., phenylpropenoyl, phenylbutenoyl, phenylmethacryloyl, phenylpentanoyl, phenylhexenoyl, etc.), naphthyl(C_3-C_6)alkenoyl (e.g., naphthylpropenoyl, naphthylbutenoyl, etc.), etc.];
ar(lower)alkoxycarbonyl [e.g., phenyl(C_1-C_6)alkoxycarbonyl (e.g., benzyloxycarbonyl, etc.), fluorenyl(C_1-C_6)alkoxycarbonyl (e.g., fluorenylmethyloxycarbonyl, etc.), etc.];

aryloxycarbonyl (e.g., phenoxycarbonyl, naphthyloxycarbonyl, etc.);

aryloxy(lower)alkanoyl (e.g., phenoxyacetyl, phenoxypropionyl, etc.);

arylcarbamoyl (e.g., phenylcarbamoyl, etc.);

arylthiocarbamoyl (e.g., phenylthiocarbamoyl, etc.);

arylglyoxyloyl (e.g., phenylglyoxyloyl, naphthylglyoxyloyl, etc.);

arylsulfonyl which may have 1 to 4 lower alkyl (e.g., phenylsulfonyl, p-tolylsulfonyl, etc.); or the like;

Heterocyclic acyl such as

heterocycliccarbonyl;

heterocyclic(lower)alkanoyl (e.g., heterocyclicacetyl, heterocyclicpropanoyl, heterocyclicbutanoyl, heterocyclicpentanoyl, heterocyclichexanoyl, etc.);

heterocyclic(lower)alkenoyl (e.g., heterocyclicpropenoyl, heterocyclicbutenoyl, heterocyclicpentenoyl, heterocyclichexenoyl, etc.);

heterocyclicglyoxyloyl; or the like;

in which suitable "heterocyclic" moiety in the terms "heterocycliccarbonyl", "heterocyclic(lower)alkanoyl", "heterocyclic(lower)alkenoyl" and "heterocyclicglyoxyloyl" can be referred to aforementioned "heterocyclic" moiety, and this "acyl group" may have one or more suitable substituent(s) selected from the group consisting of lower alkyl, oxo, amino and hydroxy.

Suitable example of "acyl group" of R^1 can be referred to aforementioned "acyl group", in which the preferred one may be aroyl which may have one or more suitable substituent(s), lower alkoxycarbonyl, higher alkanoyl and heterocycliccarbonyl which may have one or more suitable substituent(s).

Suitable example of "suitable substituent(s)" in the term of "aroyl substituted with one or more suitable substituent(s)"

and "heterocycliccarbonyl which may have one or more suitable substituent(s)" may be heterocyclic group substituted with aryl having lower alkoxy, heterocyclic group substituted with aryl having lower alkoxy(lower)alkoxy, heterocyclic group substituted with aryl having lower alkoxy(higher)alkoxy, heterocyclic group substituted with aryl having cyclo(lower)alkyloxy, heterocyclic group substituted with aryl having heterocyclic group, heterocyclic group substituted with cyclo(lower)alkyl having cyclo(lower)alkyl, heterocyclic group substituted with aryl having aryl substituted with lower alkoxy(lower)alkoxy, heterocyclic group substituted with aryl having heterocyclic group substituted with cyclo(lower)alkyl, heterocyclic group substituted with aryl having aryl substituted with heterocyclic group, heterocyclic group substituted with aryl having aryl substituted with lower alkoxy(lower)alkyl, heterocyclic group substituted with aryl having heterocyclic group substituted with aryl(lower)alkoxy, heterocyclic group substituted with aryl having heterocyclic group substituted with lower alkoxy and aryl having halogen, heterocyclic group substituted with aryl having aryl substituted with lower alkoxy, heterocyclic group substituted with aryl having cyclo(lower)alkyl, heterocyclic group substituted with aryl having heterocyclic group substituted with aryl, heterocyclic group substituted with aryl having heterocyclic group substituted with aryloxy, heterocyclic group substituted with aryl having heterocyclic group substituted with lower alkoxy(lower)alkoxy, heterocyclic group substituted with aryl having heterocyclic group substituted with lower alkoxy(lower)alkylthio, heterocyclic group substituted with aryl having heterocyclic higher alkoxy, heterocyclic group substituted with aryl having heterocyclic group substituted with cyclo(lower)alkyloxy, heterocyclic group substituted with aryl having heterocyclic group substituted with aryl having lower alkoxy(lower)alkoxy, heterocyclic group substituted with aryl having aryloxy(lower)alkoxy, heterocyclic group substituted

with aryl having heterocyclic group substituted with lower alkylthio, heterocyclic group substituted with aryl having heterocyclic group substituted with lower alkoxy and aryl, aryl substituted with heterocyclic group having aryl substituted with heterocyclic group, aryl substituted with lower alkoxy having cyclo(lower)alkyl and amino, aryl substituted with heterocyclic group having cyclo(lower)alkyl, aryl substituted with lower alkoxy having cyclo(lower)alkyl and protected amino, aryl substituted with heterocyclic group having lower alkyl, aryl substituted with aryl having lower alkoxy, heterocyclic group substituted with cyclo(lower)alkyl having lower alkyl, heterocyclic group substituted with cyclo(lower)alkyl having lower alkoxy and cyclo(lower)alkyl, heterocyclic group substituted with cyclo(lower)alkyl having cyclo(lower)alkyl substituted with lower alkoxy, heterocyclic group substituted with aryl having lower alkoxy(lower)alkylsulfonyl, heterocyclic group substituted with aryl having lower alkoxy(higher)alkylsulfonyl, higher alkoxy, aryl substituted with lower alkoxy(higher)alkoxy, heterocyclic group substituted with aryl having higher alkoxy, heterocyclic group substituted with higher alkyl, in which the preferred one may be unsaturated condensed heterocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having (C_4-C_6)-alkoxy, unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having (C_1-C_4)alkoxy(C_4-C_6)alkoxy, unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having (C_1-C_4)alkoxy(C_7-C_{14})alkoxy, saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl having (C_1-C_4)-alkoxy(C_7-C_{14})alkoxy, unsaturated condensed heterocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having cyclo(C_4-C_6)alkyloxy, unsaturated condensed heterocyclic group containing 1 or 2 sulfur

atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with cyclo-(C_4-C_6)alkyl having cyclo(C_4-C_6)alkyl, unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having phenyl substituted with (C_1-C_4)alkoxy(C_1-C_4)alkoxy, unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with cyclo(C_4-C_6)alkyl, unsaturated condensed heterocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) having cyclo(C_4-C_6)alkyl,

unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having (C_4-C_6)alkoxy,

unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having cyclo(C_4-C_6)alkyl,

unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having phenyl substituted with (C_1-C_4)alkoxy,

unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having phenyl substituted with (C_1-C_4)alkoxy(C_1-C_4)alkyl,

unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having phenyl substituted with saturated 3 to 8-membered heteromonocyclic group containing 1 or 2 oxygen

atom(s) and 1 to 3 nitrogen atom(s) having di(C_1-C_4)alkyl.

unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with cyclo(C_4-C_6)alkyl having (C_1-C_4)alkyl,

unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl.

unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenoxy.

unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl(C_1-C_4)alkoxy,

unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with (C_1-C_4)alkoxy and chlorophenyl,

unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) substituted with di(C_1-C_4)alkyl,

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl having (C_7-C_{14})alkoxy,

unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having (C_4-C_6)alkoxy,

unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having (C_1-C_4)alkoxy(C_4-C_6)alkoxy,

unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having (C_1-C_4)alkoxy(C_7-C_{14})alkoxy,

unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having (C_7-C_{14})alkoxy substituted with saturated 3 to 8-membered heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) having di(C_1-C_4)alkyl,

unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) substituted with di(C_1-C_4)alkyl,

unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 4 nitrogen atom(s) substituted with phenyl having (C_1-C_4)alkoxy(C_7-C_{14})-alkylsulfonyl,

saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl having (C_1-C_4)alkoxy(C_4-C_6)alkoxy,

saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl having (C_1-C_4)alkoxy substituted with phenoxy,

saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl having cyclo(C_4-C_6)alkyl,

saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl having

phenyl substituted with (C_1-C_4)alkoxy(C_4-C_6)alkoxy,

saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl having phenyl substituted with saturated 3 to 8-membered heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) substituted with di(C_1-C_4)alkyl,

saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with cyclo-(C_4-C_6)alkyloxy,

saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl,

saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl having (C_1-C_4)alkoxy(C_4-C_6)alkoxy,

saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with (C_1-C_4)alkylthio.

saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with (C_1-C_4)alkoxy(C_4-C_6)alkylthio,

saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with cyclo-(C_4-C_6)alkyl,

saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with saturated 3 to 8-membered heteromonocyclic group containing 1 or 2 oxygen atom(s),

saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with (C_1-C_4)alkoxy and phenyl,

saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with (C_1-C_4)alkoxy and chlorophenyl,

saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 4 nitrogen atom(s) substituted with di(C_1-C_4)alkyl,

saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with cyclo-(C_4-C_6)alkyl having (C_4-C_6)alkyl,

saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with cyclo-(C_4-C_6)alkyl having cyclo(C_4-C_6)alkyl and (C_1-C_4)alkoxy,

saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with cyclo-(C_4-C_6)alkyl having cyclo(C_4-C_6)alkyl substituted with (C_1-C_4)alkoxy,

unsaturated condensed heterocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having (C_1-C_4)alkoxy(C_4-C_6)alkoxy,

unsaturated condensed heterocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with

phenyl having saturated 3 to 8-membered heteromonocyclic group 1 to 4 nitrogen atom(s) substituted with (C_1-C_4)alkoxy-(C_1-C_6)alkoxy,

unsaturated condensed heterocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group 1 to 4 nitrogen atom(s) substituted with (C_1-C_4)-alkoxy(C_4-C_6)alkylthio,

unsaturated condensed heterocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) substituted with di(C_1-C_4)alkyl,

phenyl substituted with (C_1-C_4)alkoxy having cyclo-(C_4-C_6)alkyl and protected amino,

phenyl substituted with (C_1-C_4)alkoxy having cyclo-(C_4-C_6)alkyl and amino,

phenyl substituted with phenyl having (C_4-C_6)alkoxy,

phenyl substituted with unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) having (C_4-C_6)alkyl,

phenyl substituted with saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with cyclo(C_4-C_6)alkyl,

phenyl substituted with saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) having phenyl substituted with saturated 3 to 8-membered heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) having di(C_1-C_4)alkyl,

phenyl substituted with condensed heterocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) having (C_4-C_6)alkyl,

(C_7-C_{14})alkoxy,

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with

(C_7-C_{14})alkyl,

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl having (C_4-C_6)alkoxy,

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),

xylyl substituted with (C_1-C_4)alkoxy(C_7-C_{14})alkoxy, and the most preferred one may be imidazothiadiazolyl substituted with phenyl having pentyloxy, thiadiazolyl substituted with phenyl having methoxyhexyloxy, thiadiazolyl substituted with phenyl having methoxyoctyloxy, thiadiazolyl substituted with phenyl having methoxyheptyloxy, imidazothiadiazolyl substituted with phenyl having cyclohexyloxy, imidazothiadiazolyl substituted with phenyl having dimethylmorpholino, piperazinyl substituted with phenyl having methoxyheptyloxy, piperazinyl substituted with phenyl having methoxyoctyloxy, piperazinyl substituted with cyclohexyl having cyclohexyl, thiadiazolyl substituted with phenyl having phenyl substituted with methoxyethoxy, thiadiazolyl substituted with phenyl having phenyl substituted with methoxybutoxy, thiadiazolyl substituted with phenyl having phenyl substituted with ethoxypropoxy, imidazothiadiazolyl substituted with phenyl having piperazinyl substituted with cyclohexyl, imidazothiadiazolyl substituted with phenyl having piperazinyl substituted with cyclohexyl,

thiazolyl substituted with phenyl having pentyloxy,

thiadiazolyl substituted with phenyl having methoxyheptyloxy,

thiadiazolyl substituted with phenyl having cyclohexyl,

thiadiazolyl substituted with phenyl having cyclohexyloxy,

thiadiazolyl substituted with phenyl having phenyl substituted with propoxy,

thiadiazolyl substituted with phenyl having phenyl

substituted with ethoxymethyl,

thiadiazolyl substituted with phenyl having phenyl substituted with methoxypropoxy,

thiadiazolyl substituted with phenyl having piperazinyl substituted with cyclohexyl,

thiadiazolyl substituted with phenyl having phenyl substituted with dimethylmorpholino,

thiadiazolyl substituted with phenyl having piperazinyl substituted with methylcyclohexyl,

thiadiazolyl substituted with phenyl having piperidyl,

thiadiazolyl substituted with phenyl having piperidyl substituted with phenyl,

thiadiazolyl substituted with phenyl having piperidyl substituted with phenoxy,

thiadiazolyl substituted with phenyl having piperidyl substituted with benzyloxy,

thiadiazolyl substituted with phenyl having piperidyl substituted with methoxy and chlorophenyl,

thiadiazolyl substituted with phenyl having dimethylmorpholino,

pyrimidinyl substituted with phenyl having octyloxy,

isoxazolyl substituted with phenyl having pentyloxy,

isoxazolyl substituted with phenyl having methoxyhexyloxy,

isosxazolyl substituted with phenyl having methoxyheptyloxy,

isoxazolyl substituted with phenyl having heptyloxy substituted with dimethylmorpholino,

isoxazolyl substituted with phenyl having octyloxy substituted with dimethylmorpholino,

isoxazolyl substituted with phenyl having dimethylmorpholino,

oxadiazolyl substituted with phenyl having pentyloxy,

oxadiazolyl substituted with phenyl having methoxyheptyloxy,

oxadiazolyl substituted with phenyl having methoxynonyloxy,

oxadiazolyl substituted with phenyl having methoxyheptylsulfonyl,

oxadiazolyl substituted with phenyl having methoxynonylsulfonyl,

piperazinyl substituted with phenyl having methoxyhexyloxy,

piperazinyl substituted with phenyl having methoxyheptyloxy,

piperazinyl substituted with phenyl having phenoxypropoxy,

piperazinyl substituted with phenyl having cyclohexyl,

piperazinyl substituted with phenyl having phenyl substituted with methoxypentyloxyphenyl,

piperazinyl substituted with phenyl having phenyl substituted with dimethylmorpholino,

piperazinyl substituted with phenyl having piperidyl substituted with cyclohexyloxy,

piperazinyl substituted with phenyl having piperidyl substituted with phenyl,

piperazinyl substituted with phenyl having piperidyl substituted with methoxybutoxyphenyl,

piperazinyl substituted with phenyl having piperidyl substituted with propylthio,

piperazinyl substituted with phenyl having piperidyl substituted with methoxyhexylthio,

piperazinyl substituted with phenyl having piperidyl substituted with cyclobutanespiro,

piperazinyl substituted with phenyl having piperidyl substituted with dioxacyclobutanespiro,

piperazinyl substituted with phenyl having piperidyl substituted with methoxy and phenyl,

piperazinyl substituted with phenyl having piperidyl substituted with methoxy and chlorophenyl,

piperazinyl substituted with phenyl having dimethylmorpholino,

piperazinyl substituted with cyclohexyl having tert-butyl,

piperazinyl substituted with cyclohexyl having cyclohexyl and methoxy,

piperazinyl substituted with cyclohexyl having cyclohexyl substituted with propoxy,

imidazothiadiazolyl substituted with phenyl having methoxybutoxy,

imidazolthiadiazolyl substituted with phenyl having cyclohexyloxy,

imidazothiadiazolyl substituted with phenyl having piperazinyl substituted with cyclohexyl,

imidazolthiadiazolyl substituted with phenyl having piperidyl substituted with methoxypropoxy,

imidazothiadiazolyl substituted with phenyl having piperidyl substituted with methoxybutoxy,

imidazothiadiazolyl substituted with phenyl having piperidyl substituted with methoxypentyloxy,

imidazothiadiazolyl substituted with phenyl having piperidyl substituted with methoxyhexyloxy,

imidazothiadiazolyl substituted with phenyl having piperidyl substituted with methoxyhexylthio,

imidazothiadiazolyl substituted with phenyl having dimethylmorpholino,

phenyl substituted with propoxy having cyclohexyl and tert-butoxycarbonylamino,

phenyl substituted with propoxy having cyclohexyl and amino,

phenyl substituted with phenyl having pentyloxy,

phenyl substituted with thiazolyl having pentyl,

phenyl substituted with piperazinyl having cyclohexyl,

phenyl substituted with piperazinyl having phenyl substituted with dimethylmorpholino,

phenyl substituted with bezoxazolyl having pentyl,
octyloxy,
pyrazolyl substituted with decyl,
pyrazolyl substituted with phenyl having hexyloxy,
pyrazolyl substituted with phenyl having piperidyl,
xylyl substituted with methoxyheptyloxy.

The more suitable example of "acyl group" may be benzoyl which has imidazolthiadiazolyl substituted with phenyl having pentyloxy, benzoyl which has thiadiazolyl substituted with phenyl having methoxyhexyloxy, benzoyl which has thiadiazolyl substituted with phenyl having methoxyoctyloxy, benzoyl which has thiadiazolyl substituted with phenyl having methoxyheptyloxy, benzoyl which has imidazothiadiazolyl substituted with phenyl having cyclohexyloxy, benzoyl which has imidazothiadiazolyl substituted with phenyl having dimethylmorpholino, benzoyl which has piperazinyl substituted with phenyl having methoxyheptyloxy, benzoyl which has piperazinyl substituted with phenyl having methoxyoctyloxy, benzoyl which has piperazinyl substituted with cyclohexyl having cyclohexyl, benzoyl which has thiadiazolyl substituted with phenyl having phenyl substituted with methoxyethoxy, benzoyl which has thiadiazolyl substituted with phenyl having phenyl substituted with methoxybutoxy, benzoyl which has thiadiazolyl substituted with phenyl having phenyl substituted with ethoxypropoxy, benzoyl which has imidazothiadiazolyl substituted with phenyl having piperazinyl substituted with cyclohexyl, benzoyl which has imidazothiadiazolyl substituted with phenyl having piperazinyl substituted with cyclohexyl,

benzoyl which has thiazolyl substituted with phenyl having pentyloxy,

benzoyl which has thiadiazolyl substituted with phenyl having methoxyheptyloxy,

benzoyl which has thiadiazolyl substituted with phenyl having cyclohexyl,

benzoyl which has thiadiazolyl substituted with phenyl having cyclohexyloxy,

benzoyl which has thiadiazolyl substituted with phenyl having phenyl substituted with propoxy,

benzoyl which has thiadiazolyl substituted with phenyl having phenyl substituted with ethoxymethyl,

benzoyl which has thiadiazolyl substituted with phenyl having phenyl substituted with methoxypropoxy,

benzoyl which has thiadiazolyl substituted with phenyl having phenyl substituted with dimethylmorpholino,

benzoyl which has thiadiazolyl substituted with phenyl having piperazinyl substituted with cyclohexyl,

benzoyl which has thiadiazolyl substituted with phenyl having piperazinyl substituted with methylcyclohexyl,

benzoyl which has thiadiazolyl substituted with phenyl having piperidyl,

benzoyl which has thiadiazolyl substituted with phenyl having piperidyl substituted with phenyl,

benzoyl which has thiadiazolyl substituted with phenyl having piperidyl substituted with phenoxy,

benzoyl which has thiadiazolyl substituted with phenyl having piperidyl substituted with benzyloxy,

benzoyl which has thiadiazolyl substituted with phenyl having piperidyl substituted with methoxy and chlorophenyl,

benzoyl which has thiadiazolyl substituted with phenyl having dimethylmorpholino,

benzoyl which has pyrimidinyl substituted with phenyl having octyloxy,

benzoyl which has isoxazolyl substituted with phenyl having pentyloxy,

benzoyl which has isoxazolyl substituted with pentyl having methoxyhexyloxy,

benzoyl which has isoxazolyl substituted with phenyl having methoxyheptyloxy,

benzoyl which has isoxazolyl substituted with phenyl

having heptyloxy substituted with dimethylmorpholino,

benzoyl which has isoxazolyl substituted with phenyl having octyloxy substituted with dimethylmorpholino,

benzoyl which has isoxazolyl substituted with phenyl having dimethylmorpholino,

benzoyl which has oxadiazolyl substituted with phenyl having pentyloxy,

benzoyl which has oxadiazolyl substituted with phenyl having methoxyheptyloxy,

benzoyl which has oxadiazolyl substituted with phenyl having methoxynonyloxy,

benzoyl which has oxadiazolyl substituted with phenyl having methoxyheptylsulfonyl,

benzoyl which has oxadiazolyl substituted with phenyl having methoxynonylsulfonyl,

benzoyl which has piperazinyl substituted with phenyl having methoxyhexyloxy,

benzoyl which has piperazinyl substituted with phenyl having methoxyheptyloxy,

benzoyl which has piperazinyl substituted with phenyl having phenoxypropoxy,

benzoyl which has piperazinyl substituted with phenyl having cyclohexyl,

benzoyl which has piperazinyl substituted with phenyl having phenyl substituted with methoxypentyloxyphenyl,

benzoyl which has piperazinyl substituted with phenyl having phenyl substituted with dimethylmorpholino,

benzoyl which has piperazinyl substituted with phenyl having piperidyl substituted with cyclohexyloxy,

benzoyl which has piperazinyl substituted with phenyl having piperidyl substituted with phenyl,

benzoyl which has piperazinyl substituted with phenyl having piperidyl substituted with methoxybutoxyphenyl,

benzoyl which has piperazinyl substituted with phenyl having piperidyl substituted with propylthio,

benzoyl which has piperazinyl substituted with phenyl having piperidyl substituted with methoxyhexylthio,

benzoyl which has piperazinyl substituted with phenyl having piperidyl substituted with cyclobutanespiro,

benzoyl which has piperazinyl substituted with phenyl having piperidyl substituted with dioxacyclobutanespiro,

benzoyl which has piperazinyl substituted with phenyl having piperidyl substituted with methoxy and phenyl,

benzoyl which has piperazinyl substituted with phenyl having piperidyl substituted with methoxy and chlorophenyl,

benzoyl which has piperazinyl substituted with phenyl having dimethylmorpholino,

benzoyl which has piperazinyl substituted with cyclohexyl having tert-butyl,

benzoyl which has piperazinyl substituted with cyclohexyl having cyclohexyl and methoxy,

benzoyl which has piperazinyl substituted with cyclohexyl having cyclohexyl substituted with propoxy,

benzoyl which has imidazothiadiazolyl substituted with phenyl having methoxybutoxy,

benzoyl which has imidazothiadiazolyl substituted with phenyl having cyclohexyloxy,

benzoyl which has imidazothiadiazolyl substituted with phenyl having piperazinyl substituted with cyclohexyl,

benzoyl which has imidazothiadiazolyl substituted with phenyl having piperidyl substituted with methoxypropoxy,

benzoyl which has imidazothiadiazolyl substituted with phenyl having piperidyl substituted with methoxybutoxy,

benzoyl which has imidazothiadiazolyl substituted with phenyl having piperidyl substituted with methoxypentyloxy,

benzoyl which has imidazothiadiazolyl substituted with phenyl having piperidyl substituted with methoxyhexyloxy,

benzoyl which has imidazothiadiazolyl substituted with phenyl having piperidyl substituted with methoxyhexylthio,

benzoyl which has imidazothiadiazolyl substituted with

phenyl having dimethylmorpholino,

benzoyl which has phenyl substituted with propoxy having cyclohexyl and tert-butoxycarbonylamino,

benzoyl which has phenyl substituted with propoxy having cyclohexyl and amino,

benzoyl which has phenyl substituted with phenyl having pentyloxy,

benzoyl which has phenyl substituted with thiazolyl having pentyl,

benzoyl which has phenyl substituted with piperazinyl having cyclohexyl,

benzoyl which has phenyl substituted with piperazinyl having phenyl substituted with dimethylmorpholino,

benzoyl which has phenyl substituted with benzoxazolyl having pentyl,

benzoyl which has octyloxy,

thiadiazolylcarbonyl which has pyrazolyl substituted with decyl,

thiadiazolylcarbonyl which has pyrazolyl substituted with phenyl having hexyloxy,

thiadiazolylcarbonyl which has pyrazolyl substituted with phenyl having piperidyl,

piperazinylcarbonyl which has xylyl substituted with methoxyheptyloxy,

palmitoyl.

Suitable example of "lower alkyl" in the term of "lower alkyl which has one or more hydroxy or protected hydroxy" can be referred to aforementioned "lower alkyl", in which the preferred one may be methyl, ethyl, propyl, isopropyl, butyl, pentyl and hexyl.

Suitable example of "hydroxy protective group" in the term of "protected hydroxy" may include acyl (e.g., lower alkanoyl, etc.) as mentioned above, phenyl(lower)alkyl which may have one or more suitable substituent(s) (e.g., benzyl, 4-

methoxybenzyl, trityl, etc.), tri-substituted silyl [e.g., tri(lower)alkylsilyl(e.g., trimethylsilyl, t-butyldimethylsilyl, etc.), etc.], tetrahydropyranyl and the like.

Suitable example of "lower alkyl which has one or more hydroxy or protected hydroxy" may be dihydroxypropyl, dihydroxyisopropyl, trihydroxybutyl, tetrahydroxypentyl, pentahydroxyhexyl and diacetyloxyisopropyl.

Suitable example of "acyl group" of R^2 can be referred to aforementioned "acyl group", in which the preferred one may be "amino protective group" mentioned below, and the most preferred one may be acetyl, 2-acetyloxypropionyl, metylsulfonyl, 2,5-diaminopentanoyl, benzyloxycarbonyl, fluorenylmethoxycarbonyl, allyloxycarbonyl and tert-butoxycarbonyl.

Suitable example of "amino protective group" may be included in aforementioned "acyl group", a conventional protective group such as ar(lower)alkoxycarbonyl and lower alkoxycarbonyl, in which the preferred one may be phenyl-(C_1-C_4)alkoxycarbonyl and fluorenyl(C_1-C_4)alkoxycarbonyl and (C_1-C_4)alkoxycarbonyl, and the most preferred one may be benzyloxycarbonyl, fluorenylmethoxycarbonyl and tert-butoxycarbonyl.

Suitable example of "acyl" moiety of "acyloxy" can be referred to aforementioned "acyl group", in which the preferred one may be lower alkenyloxycarbonyl, and the most preferred one may be allyloxycarbonyl.

Suitable example of "acyloxy" may be lower alkenyloxycarbonyloxy, and the more preferred one may be allyloxycarbonyloxy.

Particularly, the preferred examples of the polypeptide compound (I) of the present invention are as follows:

the compound (I), wherein

R^1 is hydrogen or acyl group

R^2 is hydrogen,

R^3 is lower alkyl which has one or more hydroxy,

R^4 is hydrogen or hydroxy;

R^5 is hydroxysulfonyloxy; and

R^6 is hydroxy.

And the compound (I), more preferred one may be wherein

R^1 is hydrogen or acyl group

R^2 is hydrogen,

R^3 is lower alkyl which has two hydroxy,

R^4 is hydrogen or hydroxy;

R^5 is hydroxysulfonyloxy; and

R^6 is hydroxy,

The processes for preparing the polypeptide compound (I) of the present invention are explained in detail in the following.

Process 1

The object compound (Ia) or a salt thereof can be prepared by reacting the compound (II) or its reactive derivative at the amino group or a salt thereof with the compound (III) of the formula:

$$R^3=O \qquad \text{(III)}$$

or its reactive derivative, or a salt thereof.

Suitable reactive derivative of the compound (III) may include an acid halide, an acid anhydride, an activated ester, and the like. The suitable example may be an acid chloride; acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid (e.g., dialkylphosphoric acid, phenylphosphoric

acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.), dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, alkanesulfonic acid (e.g., methanesulfonic acid, ethanesulfonic acid, etc.), sulfuric acid, alkylcarbonic acid, aliphatic carboxylic acid (e.g., pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.); aromatic carboxylic acid (e.g., benzoic acid, etc.); a symmetrical acid anydride; an activated amide with imidazole, 4-substitutd imidazole, dimethylpyrazole, triazole or tetrazole; an activated ester (e.g., cyanomethyl, ester methoxymethyl ester, dimethyliminomethyl [$(CH_3)_2\overset{+}{N}=CH-$] ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenylthioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.); an ester with a N-hydroxy compound (e.g., N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxybenzotriazole, N-hydroxyphthalimide, 1-hydroxy-6-chloro-1H-benzotriazole, etc.); and the like. These reactive derivatives can optionally be selected from them according to the kind of the compound (III) to be used.

The reaction is usually carried out in a conventional solvent such as water, acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which do not adversely affect the reaction, or the mixture thereof.

When the compound (III) is used in free acid form or its salt form in the reaction, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide); N-cyclohexyl-N'-(4-

diethylaminocyclohexyl)carbodiimide; N,N'-diisopropylcarboxiimide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide; N,N-carbonyl-bis(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine, ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; isopropyl polyphosphate; phosphorous oxychloride (phosphoryl chloride); phosphorous trichloride; thionyl chloride; oxalyl chloride; triphenylphosphite; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intra-molecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, phosphorous oxychloride, etc.; or the like.

The reaction may also be carried out in the presence of an organic or inorganic base such as an alkali metal bicarbonate, tri(lower)alkylamine (e.g., triethylamine, diisopropylethylamine, etc.), pyridine, di(lower)alkylaminopyridine (e.g., 4-dimethylaminopyridine, etc.) N-(lower)alkylmorphorine, N,N-di(lower)alkylbenzylamine, or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to heating.

Process 2

The object compound (Ib) or a salt thereof can be prepared by reacting the compound (Ia) or its reactive derivative at the amino group or a salt thereof with the compound (IV) of the formula:

$$R_a^2 - OH \qquad (IV)$$

(wherein R_a^2 is acyl group)

or its reactive derivative at the carboxy group or a salt thereof.

Suitable reactive derivative of the compound (IV) may include an acid halide, an acid anhydride, an activated ester, and the like. The suitable example may be an acid chloride; acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid (e.g., dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.), dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, alkanesulfonic acid (e.g., methanesulfonic acid, ethanesulfonic acid, etc.), sulfuric acid, alkylcarbonic acid, aliphatic carboxylic acid (e.g., pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.); aromatic carboxylic acid (e.g., benzoic acid, etc.); a symmetrical acid anydride; an activated amide with imidazole, 4-substitutd imidazole, dimethylpyrazole, triazole or tetrazole; an activated ester (e.g., cyanomethyl, ester methoxymethyl ester, dimethyliminomethyl [$(CH_3)_2\overset{+}{N}=CH-$] ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenylthioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.); an ester with a N-hydroxy compound (e.g., N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxybenzotriazole, N-hydroxyphthalimide, 1-hydroxy-6-chloro-1H-benzotriazole, etc.); and the like. These reactive derivatives can optionally be selected from them according to the kind of the compound (IV) to be used.

The reaction is usually carried out in a conventional solvent such as water, acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which do not adversely affect the reaction, or the mixture thereof.

When the compound (IV) is used in free acid form or its salt form in the reaction, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide); N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diisopropylcarboximide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide; N,N-carbonyl-bis(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine, ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; isopropyl polyphosphate; phosphorous oxychloride (phosphoryl chloride); phosphorous trichloride; thionyl chloride; oxalyl chloride; triphenylphosphite; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intra-molecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, phosphorous oxychloride, etc.; or the like.

The reaction may also be carried out in the presence of an organic or inorganic base such as an alkali metal bicarbonate, tri(lower)alkylamine (e.g., triethylamine, diisopropylethylamine, etc.), pyridine, di(lower)alkylaminopyridine (e.g., 4-dimethylaminopyridine, etc.) N-(lower)alkylmorphorine, N,N-di(lower)alkylbenzylamine, or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to heating.

Process 3

The object compound (Ia) or a salt thereof can be prepared by subjecting a compound (Ib) or a salt thereof to elimination reaction of the acyl group.

This reaction is carried out in accordance with a conventional method such as hydrolysis, reduction or the like.

The hydrolysis is preferably carried out in the presence of a base or an acid including Lewis acid. Suitable base may include an inorganic base and an organic base such as an alkali metal [e.g. sodium, potassium, etc.], an alkaline earth metal [e.g. magnesium, calcium, etc.], the hydroxide or carbonate or bicarbonate thereof, trialkylamine [e.g. trimethylamine, triethylamine, etc.], picoline, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]undec-7-ene, or the like.

Suitable acid may include an organic acid [e.g. formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.] and an inorganic acid [e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, etc.]. The elimination using Lewis acid such as trihaloacetic acid [e.g. trichloroacetic acid, trifluoroacetic acid, etc.] or the like is preferably carried out in the presence of cation trapping agents [e.g. anisole, phenol, etc.].

The reaction is usually carried out in a solvent such as water, an alcohol [e.g. methanol, ethanol, etc.], methylene chloride, tetrahydrofuran, a mixture thereof or any other solvent which does not adversely influence the reaction. A liquid base or acid can be also used as the solvent. The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

The reduction method applicable for the elimination reaction may include chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction are a combination of metal [e.g. tin, zinc, iron, etc.] or metallic compound [e.g. chromium chloride, chromium acetate, etc.] and an organic or inorganic acid [e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.].

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts [e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.], palladium catalysts [e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium, sulfate, palladium on barium carbonate, etc.], nickel catalysts [e.g. reduced nickel, nickel oxide, Raney nickel, etc.], cobalt catalysts [e.g. reduced cobalt, Raney cobalt, etc], iron catalysts [e.g. reduced iron, Raney iron, etc], copper catalysts [e.g. reduced copper, Raney copper, Ullman copper, etc.] and the like.

The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, N,N-dimethylformamide, or a mixture thereof. Additionally, in case that the above-mentioned acids to be used in chemical reduction are in liquid, they can also be used as a solvent. Further, a suitable solvent to be used in catalytic reduction may be the above-mentioned solvent, and other conventional solvent such as diethyl ether, dioxane, tetrahydrofuran, etc., or a mixture thereof.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to warming.

Process 4

The object compound (Id) or a salt thereof can be prepared by reacting the compound (Ic) or its reactive derivative at the amino group or a salt thereof with the compound (V) of the formula:

$$R_a^1 - OH \qquad (V)$$

(wherein R_a^1 is acyl group)

or its reactive derivative at the carboxy group or a salt thereof.

Suitable reactive derivative at the carboxy group of the compound (V) may include an acid halide, an acid anhydride, an

activated amide, an activated ester, and the like. Suitable examples of the reactive derivatives may be an acid chloride; an acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid [e.g., dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.], dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, sulfonic acid [e.g., methanesulfonic acid, etc.], aliphatic carboxylic acid [e.g., acetic acid, propionic acid, butyric acid, isobutyric acid, pivaric acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid trichloroacetic acid, etc.]; or aromatic carboxylic acid [e.g., benzoic acid, etc.]; a symmetrical acid, anhydride;
an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole, tetrazole or 1-hydroxy-1H-benzotriazole; or an activated ester [e.g., cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl [$(CH_3)_2\overset{+}{N}=CH-$] ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachloropentyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.], or
an ester with a N-hydroxy compound [e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxy-1H-benzotriazole, etc.], and the like. These reactive derivatives can optionally be selected from them according to the kind of the compound (V) to be used.

Suitable salts of the compound (V) and its reactive derivative can be referred to the ones as exemplified for the polypeptide compound (I).

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g., methanol, ethanol, etc.], acetone, dioxane, acetonitrile, chloroform, methylene chloride,

ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. These conventional solvent may also be used in a mixture with water.

In this reaction, when the compound (V) is used in a free acid form or its salt form, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diethylcarbodiimide; N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide; N,N-carbonylbis-(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine, ethoxyacetylene; 1-alkoxy-2-chloroethylene; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride); phosphorus trichloride; thionyl chloride; oxalyl chloride; lower alkyl haloformate [e.g., ethyl chloroformate, isopropyl chloroformate, etc.]; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intramolecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, trichloromethyl chloroformate, phosphorous oxychloride, methanesulfonyl chloride, etc.; or the like.

The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal carbonate, alkali metal bicarbonate, tri(lower)alkylamine (e.g., triethylamine, diisopropylethylamine, etc.), pyridine, di(lower)alkylaminopyridine (e.g., 4-dimethylaminopyridine, etc.), N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

The compounds obtained by the above Processes 1 to 4 can be isolated and purified by a conventional method such as pulverization, recrystallization, column-chromatography, high-performance liquid chromatography (HPLC), reprecipitation, desalting resin column chromatography, or the like.

The compounds obtained by the above Processes 1 to 4 may be obtained as its solvate, such as hydrate, and its solvate, such as hydrate is included within the scope of the present invention.

It is to be noted that each of the polypeptide compound (I) may include one or more stereoisomer such as optical isomer(s) and geometrical isomer(s) due to asymmetric carbon atom(s) and double bond(s) and all such isomers and the mixture thereof are included within the scope of the present invention.

The polypeptide compound (I) or a salt thereof may include solvated compound [e.g., enclosure compound (e.g., hydrate, etc.)].

The polypeptide compound (I) or a salt thereof may include both its crystal form and non-crystal form.

It should be understood that the polypeptide compound (I) of the present invention may include the prodrug form.

The patent applications and publications cited herein are incorporated by reference.

In order to show the usefulness of the polypeptide compound (I) of the present invention, the biological data of the representative compound is explained in the following.

Biological property of the polypeptide compound (I) of the present invention

Test (Antimicrobial activity):

In vitro antimicrobial activity of the object compound of

Example 4 and 9 disclosed later was determined by MIC_s in mouse serum as described below.

Test Method:

The MIC_s in mouse serum were determined by the microdilution method using ICR mouse serum buffered with 20 mM HEPES buffer (pH 7.3) as a test medium. Inoculum suspension of 10^6 cells/ml were prepared by a hemocytometric procedure and diluted to obtain an inoculum size of approximately 1.0×10^3 cells/ml. Microplates were incubated at 37°C for 24 hours in 5% CO_2. The MIC_s were defined as the lowest concentrations at which no visible growth was observed.

Test Result:

MIC (μg/ml)

Test organism / Test compound	Candida albicans FP-633
The object compound of Example 4	< 0.3
The object compound of Example 9	< 0.3
The object compound of Example 25	< 0.3
The object compound of Example 30	< 0.3

From the test result, it is realized that the polypeptide compound (I) of the present invention has an antimicrobial activity (especially, antifungal activity).

In more details, the polypeptide compound (I) of the present invention have an antifungal activity, particularly against the following fungi.

Acremonium;
Absidia (e.g., *Absidia corymbifera*, etc);
Aspergillus (e.g., *Aspergillus clavatus, Aspergillus flavus, Aspergillus fumigatus, Aspergillus nidulans, Aspergillus niger, Aspergillus terreus, Aspergillus versicolor*, etc); *Blastomyces* (e.g., *Blastomyces dermatitidis*, etc);
Candida (e.g., *Candida albicans, Candida glabrata, Candida guilliermondii, Candida kefyr, Candida krusei, Candida parapsilosis, Candida stellatoidea, Candida tropicalis, candida utilis*, etc.);
Cladosporium (e.g., *Cladosporium trichloides*, etc);
Coccidioides (e.g., *Coccidioides immitis*, etc);
Cryptococcus (e.g., *Cryptococcus neoformans*, etc);
Cunninghamella (e.g., *Cunninghamella elegans*, etc);
Dermatophyte;
Exophiala (e.g., *Exophiala dermatitidis, Exophiala spinifera*, etc);
Epidermophyton (e.g., *Epidermophyton floccosum*, etc);
Fonsecaea (e.g., *Fonsecaea pedrosoi*, etc);
Fusarium (e.g., *Fusarium solani*, etc);
Geotrichum (e.g., *Geotrichum candiddum*, etc);
Histoplasma (e.g., *Histoplasma capsulatum var. capsulatum*, etc).
Malassezia (e.g., *Malassezia furfur*, etc);
Microsporum (e.g., *Microsporum canis, Microsporum gypseum*, etc);
Mucor;
Paracoccidioides (e.g., *Paracoccidioides brasiliensis*, etc);
Penicillium (e.g., *Penicillium marneffei*, etc);
Phialophora;
Pneumocystis (e.g., *Pneumocystis carinii*, etc);
Pseudallescheria (e.g., *Pseudallescheria boydii*, etc);
Rhizopus (e.g., *Rhizopus microsporus var. rhizopodiformis, Rhizopus oryzae*, etc);
Saccharomyces (e.g., *Saccharomyces cerevisiae*, etc);
Scopulariopsis;

Sporothrix (e.g., *Sporothrix schenckii*, etc);
Trichophyton (e.g., *Trichophyton mentagrophytes*, *Trichophyton rubrum*, etc);
Trichosporon (e.g., *Trichosporon asahii*, *Trichosporon cutaneum*, etc).

The above fungi are well-known to cause various infection diseases in skin, hair, nail, oral mucosa, gastrointestinal tract, bronchus, lung, endocardium, brain, meninges, urinary organ, vaginal protion, oral cavity, ophthalmus, systemic, kidney, bronchus, heart, external auditory canal, bone, nasal cavity, paranasal cavity, spleen, liver, hypodermal tissue, lymph doct, gastrointestine, articulation, muscle, tendon, interstitial plasma cell in lung, and so on.

Therefore, the polypeptide compound (I) of the present invention are useful for preventing and treating various infectious diseases, such as dermatophytosis (e.g., trichophytosis, etc), pityriasis versicolor, candidiasis, cryptococcosis, geotrichosis, trichosporosis, aspergillosis, penicilliosis, fusariosis, zygomycosis, sporotrichosis, chromomycosis, coccidioidomycosis, histoplasmosis, blastomycosis, paracoccidioidomycosis, pseudallescheriosis, mycetoma, mycotic keratitis, otomycosis, pneumocystosis, and so on.

The combination use of azoles such as fluconazole, voriconazole, itraconazole, ketoconazole, miconazole, ER 30346 and SCH 56592; polyenes such as amphotericin B, nystatin, liposamal and lipid forms thereof such as Abelcet, AmBisome, and Amphocil; purine or pyrimidine nucleotide inhibitors such as flucytosine; or polyxins such as nikkomycines, in particular nikkomycine Z or nikkomycine X; other chitin inhibitors; elongation factor inhibitors such as sordarin and analogs thereof; mannan inhibitors such as predamycin,

bactericidal/permeability-inducing (BPI) protein products such as XMP.97 or XMP.127; or complex carbohydrate antifungal agents such as CAN-296; with the polypeptide compound (I) or a salt thereof is effective against above infectious diseases.

The pharmaceutical composition of the present invention can be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains the polypeptide compound (I) or a pharmaceutically acceptable salt thereof, as an active ingredient in admixture with an organic or inorganic carrier or excipient which is suitable for rectal; pulmonary (nasal or buccal inhalation); ocular; external (topical); oral administration; parenteral (including subcutaneous, intravenous and intramuscular) administrations; insufflation (including aerosols from metered dose inhalator); nebulizer; or dry powder inhalator.

The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers in a solid form such as granules, tablets, dragees, pellets, troches, capsules, or suppositories; creams; ointments; aerosols; powders for insufflation; in a liquid form such as solutions, emulsions, or suspensions for injection; ingestion; eye drops; and any other form suitable for use. And, if necessary, there may be included in the above preparation auxiliary substance such as stabilizing, thickening, wetting, emulsifying and coloring agents; perfumes or buffer; or any other commonly may be used as additives.

The polypeptide compound (I) or a pharmaceutically acceptable salt thereof is/are included in the pharmaceutical composition in an amount sufficient to produce the desired antimicrobial effect upon the process or condition of diseases.

For applying the composition to humans, it is preferable to apply it by intravenous, intramuscular, pulmonary, oral administration, eye drop administration or insufflation. While the dosage of therapeutically effective amount of the polypeptide

compound (I) varies from and also depends upon the age and condition of each individual patient to be treated, in the case of intravenous administration, a daily dose of 0.01-20 mg of the polypeptide compound (I) per kg weight of human being in the case of intramuscular administration, a daily dose of 0.1-20 mg of the polypeptide compound (I) per kg weight of human being, in case of oral administration, a daily dose of 0.5-50 mg of the polypetide compound (I) per kg weight of human being is generally given for treating or preventing infectious diseases.

Especially in case of the treatment of prevention of Pneumocystis carinii infection, the followings are to be noted.

For administration by inhalation, the compounds of the present invention are conveniently delivered in the form of an aerosol spray presentation form pressurized as powders which may be formulated and the powder compositions may be inhaled with the aid of an insufflation powder inhaler device. The preferred delivery system for inhalation is a metered dose inhalation aerosol, which may be formulated as a suspension or solution of compound in suitable propellants such as fluorocarbons or hydrocarbons.

Because of desirability to directly treat lung and bronchi, aerosol administration is a preferred method of administration. Insufflation is also a desirable method, especially where infection may have spread to ears and other body cavities.

Alternatively, parenteral administration may be employed using drip intravenous administration.

The following Preparations and Examples are given for the purpose of illustrating the present invention in more detail.

Preparation 1

To a solution of 1-N-t-butyloxycarbonyl-4-hydroxypiperidine (5.0 g) in dimethylformamide (DMF) (25 ml) was portionwise added sodium hydride (60% in oil) (1.29 g) with stirring under ice-cooling. The mixture was successively stirred at ambient temperature for 30 minutes, stirred at 60°C for 1 hour and cooled with an ice bath. To the reaction mixture was added 1,5-dibromopentane (6.72 ml), and the mixture was stirred at ambient temperature for 3 hours. The reaction solution was poured into water (100 ml) and extracted twice with a mixture of ethyl acetate (80 ml) and n-hexane (30 ml). The extract was washed with saturated aqueous sodium chloride, dried over magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (200 ml) eluting with a mixture of n-hexane and ethyl acetate (5:1 v/v). The fractions containing the desired compound were collected and evaporated under reduced pressure to give 4-(5-bromopentyloxy)-1-N-t-butoxycarbonylpiperidine (2.44 g).

NMR ($CDCl_3$, δ): 1.46 (9H, s), 1.50-1.70 (6H, m), 1.70-1.96 (4H, m), 3.00-3.15 (2H, m), 3.35-3.50 (5H, m), 3.70-3.90 (2H, m)

APCI MASS (m/z): 250 (M^+-101)

Preparation 2

To a solution of 4-(5-bromopentyloxy)-1-N-t-butoxycarbonylpiperidine (2.44 g) in methanol (13 ml) was added 28% sodium methoxide methanol solution (14.2 ml), and the mixture was stirred under reflux for 4 hours. The reaction mixture was evaporated in vacuo. The resulting residue was chromatographed on silica gel (250 ml) eluting with a mixture of n-hexane and ethyl acetate (5:1 v/v). The fractions containing the object compound were collected and evaporated under reduced pressure to give 4-(5-methoxypentyloxy)-1-N-t-butoxycarbonylpiperidine (1.97 g).

NMR ($CDCl_3$, δ): 1.45 (9H, s), 1.45-1.95 (10H, m), 3.03 (1H,

dd, J=3.47 and 9.20Hz), 3.10 (1H, dd, J=3.47 and 9.20Hz), 3.44 (3H, s), 3.34-3.50 (5H, m), 3.70-3.85 (2H, m)

APCI MASS (m/z): 202 (M^+-101)

Preparation 3

To a solution of 4-(5-methoxypentyloxy)-1-N-t-butoxycarbonylpiperidine (1.97 g) in ethyl acetate (20 ml) was added 4N-hydrogen chloride ethyl acetate solution (16.3 ml), and the mixture was stirred at ambient temperature for 2 hours. The reaction mixture was evaporated in vacuo. The resulting residue was dissolved in a mixture of dichloromethane and methanol (10:1; 50 ml:5 ml). To this solution was added 1N-sodium hydroxide (5 ml) with stirring. The organic layer was separated and evaporated under reduced pressure to give 4-(5-methoxypentyloxy)-piperidine (0.62 g).

NMR ($CDCl_3$, δ): 1.25-1.50 (2H, s), 1.50-1.75 (6H, m), 1.9-2.10 (2H, m), 2.70-2.90 (2H, m), 2.95-3.20 (2H, m), 3.33 (3H, s), 3.35-3.50 (5H, m)

APCI MASS (m/z): 202 (M^+)

Preparation 4

A solution of 4-fluorobenzonitrile (0.38 g), 4-(5-methoxypentyloxy)piperidine (0.62 g) and potassium carbonate (0.87 g) in DMF (8 ml) was stirred at 90-95°C for 6 hours. The reaction mixture was poured into water (50 ml) and extracted twice with a mixture of ethyl acetate and n-hexane (50ml:20 ml). The extracts were combined, washed with saturated aqueous sodium chloride, dried over magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (100 ml) eluting with a mixture of n-hexane and ethyl acetate (5:1 v/v - 2:1 v/v). The fractions containing the desired compound were collected and evaporated under reduced pressure to give 4-(5-methoxypentyloxy)-N-(4-cyanophenyl)piperidine (294 mg).

NMR ($CDCl_3$, δ): 1.35-1.55 (2H, s), 1.55-1.75 (5H, m),

1.85-2.05 (2H, m), 3.13 (1H, dd, J=3.47 and 9.20Hz), 3.17 (1H, dd, J=3.47 and 9.20Hz), 3.33 (3H, s), 3.35-3.75 (8H, m), 6.85 (2H, d, J=9.01Hz), 7.47 (2H, d, J=8.96Hz)

APCI MASS (m/z): 303 (M^+)

Preparation 5

A solution of 4-(5-methoxypentyloxy)-N-(4-cyanophenyl)piperidine (294 mg) and thiosemicarbazide (0.68 g) in toluene (20 ml) and trifluoroacetic acid (10 ml) was stirred at 60-65°C for 7 hours. After cooling, the reaction mixture was poured into a mixture of water (100 ml) and ethyl acetate (200 ml) and adjusted to pH 10 with 1N-sodium hydroxide. The mixture was dissolved in a mixture of THF (50 ml) and methanol (10 ml). The organic layer was separated, washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and evaporated in vacuo. The resulting precipitate was washed with isopropyl ether and dried in vacuo to give 2-amino-5-[4-[4-(5-methoxypentyloxy)-piperidin-1-yl]phenyl]-1,3,4-thiadiazole (1.29 g).

NMR ($CDCl_3$+CD_3OD, δ): 1.30-1.50 (2H, m), 1.50-1.80 (6H, m), 1.90-2.10 (2H, m), 2.9-3.10 (2H, m), 3.34 (3H, s), 3.35-3.70 (7H, m), 6.93 (2H, d, J=8.91Hz), 7.63 (2H, d, J=8.83Hz)

APCI MASS (m/z): 377 (M^+)

Preparation 6

To a suspension of 2-amino-5-[4-[4-(5-methoxypentyloxy)piperidin-1-yl]phenyl]-1,3,4-thiadiazole (1.29 g) in ethanol (20 ml) was added ethyl 4-bromoacetylbenzoate (1.39 g) and stirred at reflux for 5 hours. The reaction mixture was cooled and poured into diisopropyl ether (IPE) (60 ml). The resulting precipitate was collected by filtration and dried. To a suspension of the precipitate in xylene (40 ml) was added trifluoroacetic acid (4 ml), and the mixture was stirred at reflux

(130°C) for 5 hours. The reaction mixture was cooled and poured into IPE (300 ml). The resulting precipitate was filtered and dried to give 4-[2-[4-[4-(5-methoxypentyloxy)piperidin-1-yl]phenyl]imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoic acid ethyl ester trifluoroacetic acid salt (2.01 g).

NMR ($CDCl_3$, δ): 1.42 (3H, t, J=7.12Hz), 1.45-1.75 (6H, m), 1.85-2.10 (2H, m), 2.30-2.50 (2H, m), 3.36 (3H, s), 3.35-3.55 (5H, m), 3.60-3.80 (2H, m), 4.40 (2H, q, J=7.14Hz), 7.57 (2H, d, J=8.78 Hz), 7.84 (2H, d, J=8.40Hz), 7.91 (2H, d, J=8.79Hz), 8.13 (1H, s)

APCI MASS (m/z): 549 (M^++1)

Preparation 7

To a solution of 4-[2-[4-[4-(5-methoxypentyloxy)-piperidin-1-yl]phenyl]imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoic acid ethyl ester trifluoroacetic acid salt (2.01 g) in a mixture of methanol (40 ml) and tetrahydrofuran (20 ml) was added 4N-NaOH (20 ml), and the mixture was refluxed for 6 hours. The reaction mixture was cooled, poured into water (200 ml) and adjusted to pH 2 with conc. HCl. The resulting precipitate was collected by filtration, washed in turn with water, isopropyl alcohol (30 ml) and IPE (50 ml) to give 4-[2-[4-[4-(5-methoxypentyloxy)piperidin-1-yl]phenyl]-imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoic acid (1.28 g).

ESI MASS (m/z)(Negative): 519.2 (M^++1)

Preparation 8

To a solution of 4-[2-[4-[4-(5-methoxypentyloxy)-piperidin-1-yl]phenyl]imidazo[2,1-b][1,3,4]thiadiazol-6-yl]benzoic acid (1.28 g) and 1-hydroxybenzotriazole (465 mg) in dichloromethane (50 ml) was added 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (WSCD·HCl) (943 mg), and the mixture was stirred overnight at ambient temperature. The reaction mixture was evaporated in vacuo. To the resulting precipitate was added water (50 ml) and filtered. The precipitate

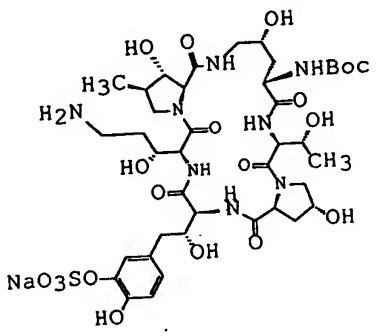
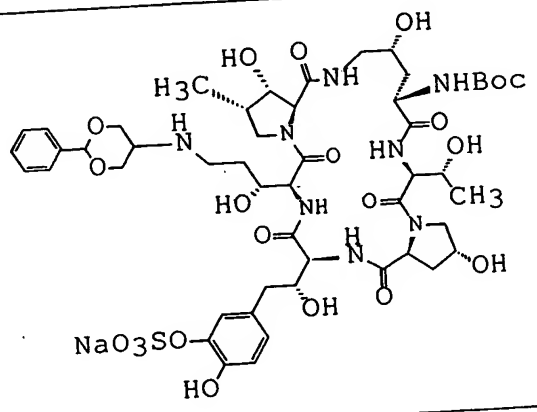
was washed with water and IPE (50 ml) and dried under reduced pressure for 3 hours to give 4-[2-[4-[4-(5-methoxypentyloxy)piperidin-1-yl]phenyl]imidazo-[2,1-b][1,3,4]thiadiazol-6-yl]benzoic acid benzotriazol-1-yl ester (1.26 g).

IR (KBr): 1774.2, 1708,6, 1604.5, 1471.4, 1365.4, 1230.4 cm^{-1}

NMR ($CDCl_3$, δ): 1.30-1.80 (8H, m), 1.85-2.10 (2H, m), 3.05-3.30 (2H, m), 3.33 (3H, s), 3.35-3.55 (4H, m), 3.55-3.75 (2H, m), 6.94 (2H, d, J=8.94Hz), 7.30-7.60 (3H, m), 7.73 (2H, d, J=8.79Hz), 8.00-8.20 (4H, m), 8.30 (2H, d, J=8.46Hz)

ESI MASS (m/z)(Positive): 660.1 (M^++Na)

The Starting Compounds used and the Object Compounds obtained in the following Preparation 9 is given in the table as below, in which the formula of the starting compound is in the upper column and the formula of the object compound are in the lower column, respectively.

Preparation No.	Formula
9	
	

Preparation 9

To a solution of a mixture of the starting compound (9) (5.4 g), 2-oxo-1,3-diacetoxypropane (4.85 g) and acetic acid (0.78 ml) in a mixture of methanol (80 ml) and dimethylformamide (40 ml) was added sodium cyanoborohydride (1.71 g) with stirring at ambient temperature, and the mixture was stirred at the same temperature overnight. The reaction mixture was concentrated in vacuo. To the resulting residue was added pH 6.86 standard buffer solution (100 ml) and acetonitrile (20 ml), and the solution was adjusted pH to 8.5 with 1N sodium hydroxide. The solution was subjected to column chromatography on ODS (Daiso-gel, SP-120-40/60-ODS-B (Trademark: prepared by Daiso Co., Ltd.)) (400 ml) eluting in turn with water, 20% acetonitrile in water and 25% acetonitrile in water. The fractions containing the object

compound were collected and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give the object compound (9) (4.44 g).

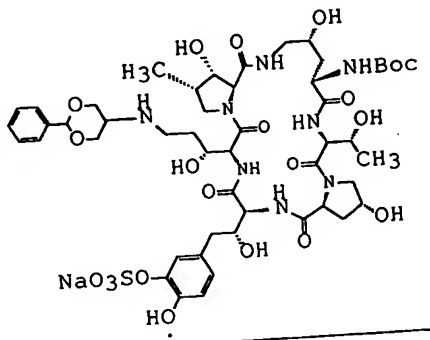
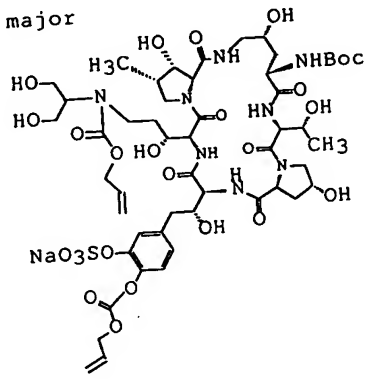
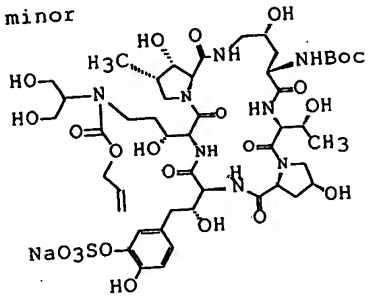
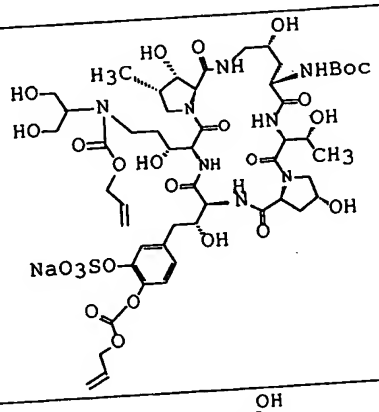
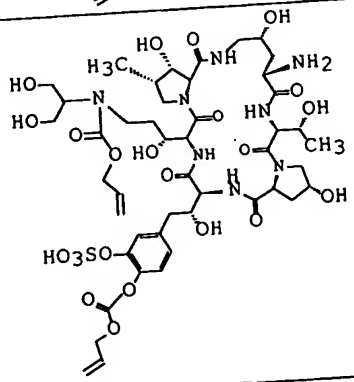
IR (KBr): 1632, 1516, 1452, 1273, 1248 cm^{-1}

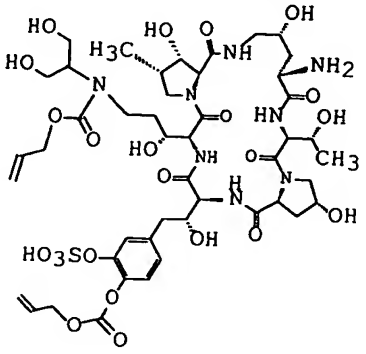
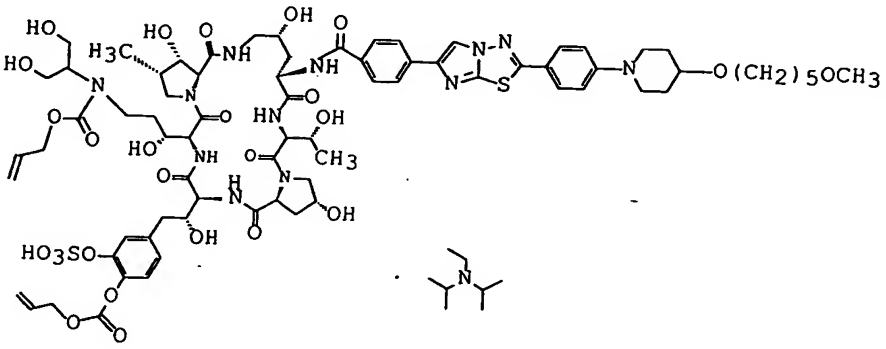
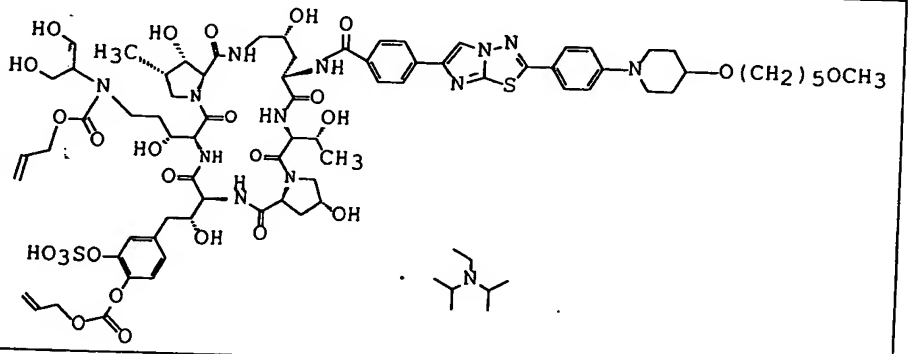
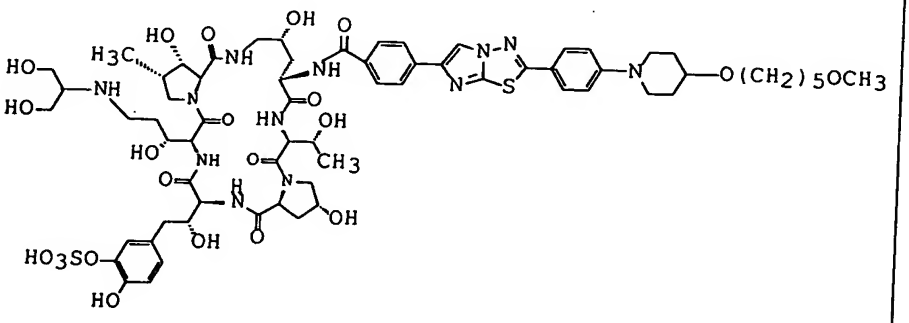
NMR (DMSO-d_6, δ): 0.98 (3H, d, J=6.88Hz), 1.11 (3H, d, J=5.64Hz), 1.36 (9H, s), 1.40-2.00 (6H, m), 2.50-2.95 (4H, m), 3.30-3.55 (2H, m), 3.65-4.45 (16H, m), 4.70-4.85 (2H, m), 5.36 (1H, s), 6.71 (1H, d, J=8.05Hz), 6.77 (1H, d, J=8.29Hz), 6.99 (1H, s), 7.30-7.45 (5H, m)

APCI MASS (m/z)(Positive): 1175.4 (M^++Na)

Elemental Analysis Calcd. for $C_{50}H_{72}N_8O_{21}S \cdot 5H_2O$:
C 46.80, H 6.52, N 8.73
Found: C 47.06, H 6.44, N 8.54

The Starting Compounds used and the Object Compounds obtained in the following Examples 1 to 53 are given in the table as below, in which the formulas of the starting compounds are in the upper column, and the formulas of the object compounds are in the lower column, respectively.

Example No.	Formula
1	
	major  minor 
2	
	

Example No.	Formula
3	
	
4	
	

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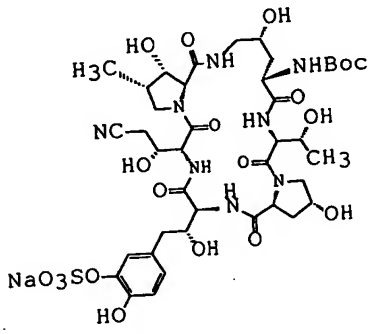
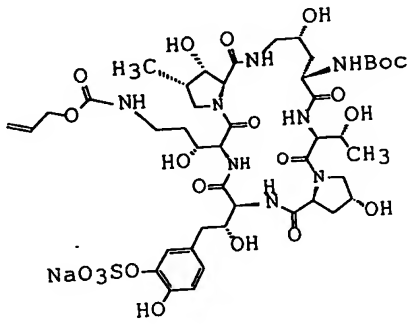
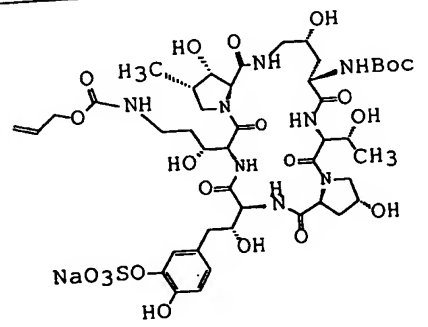
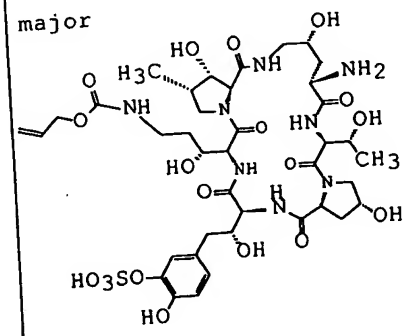
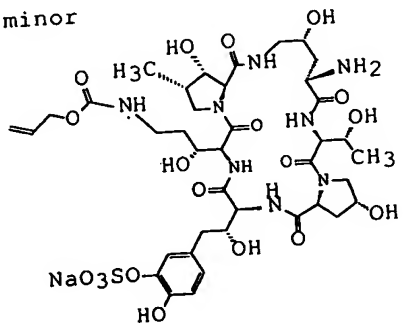
5	
	
6	
	major  minor 

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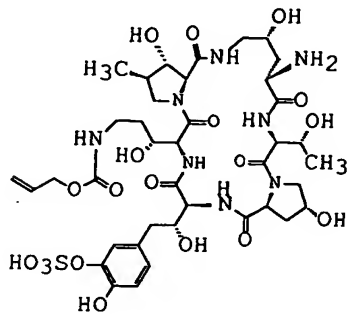
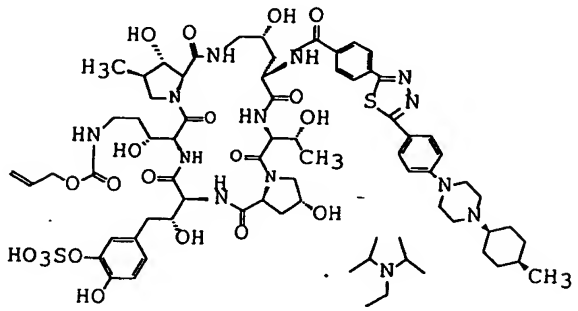
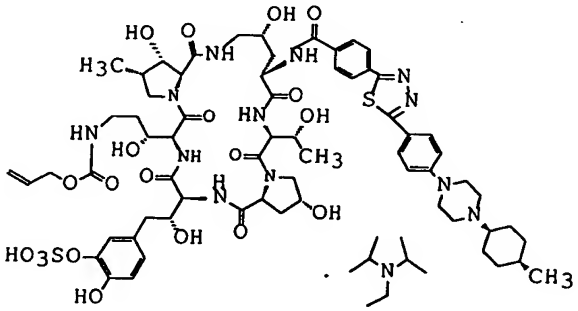
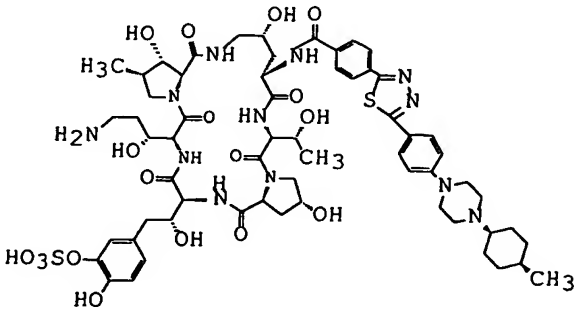
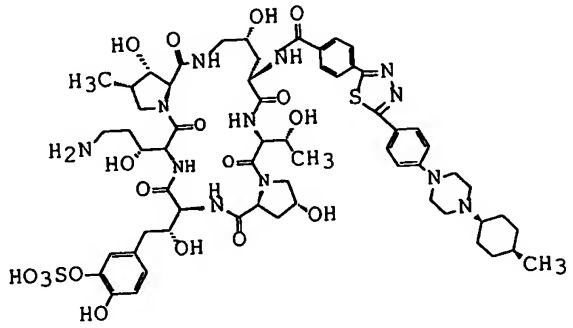
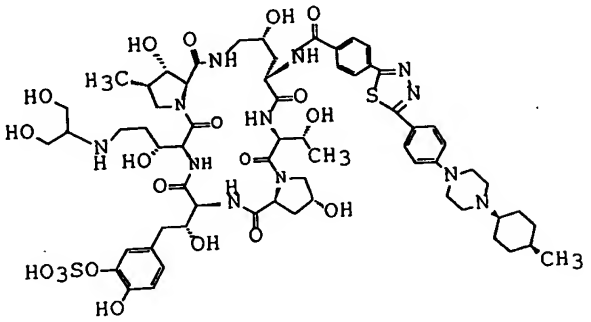
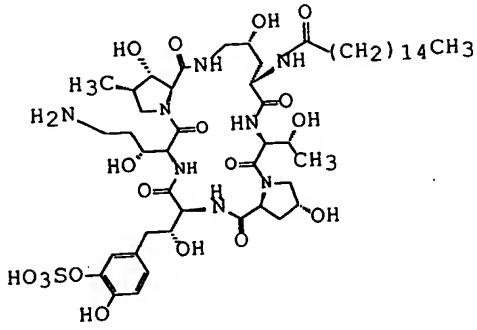
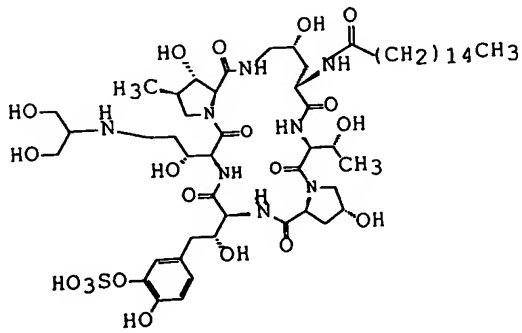
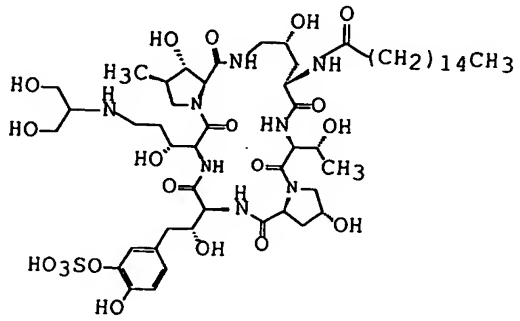
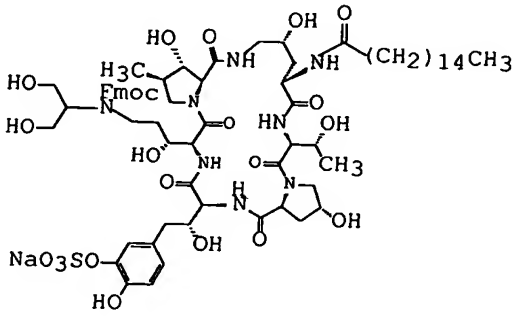
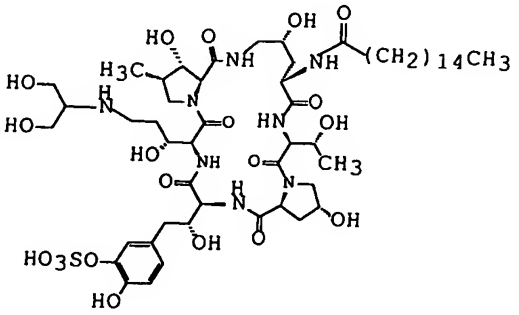
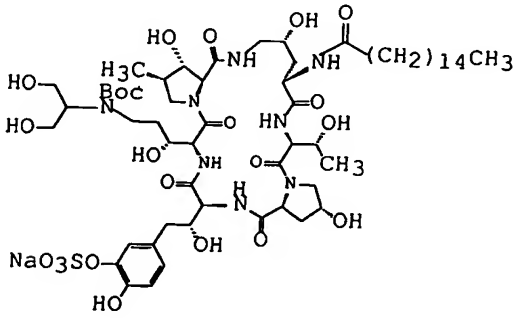
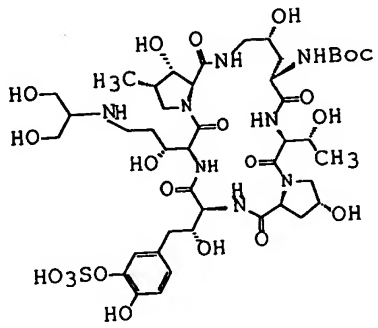
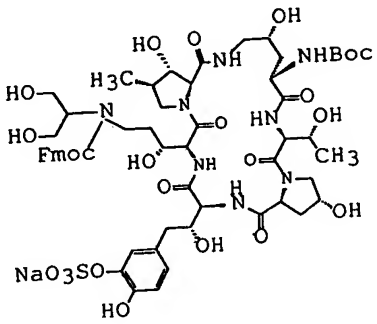
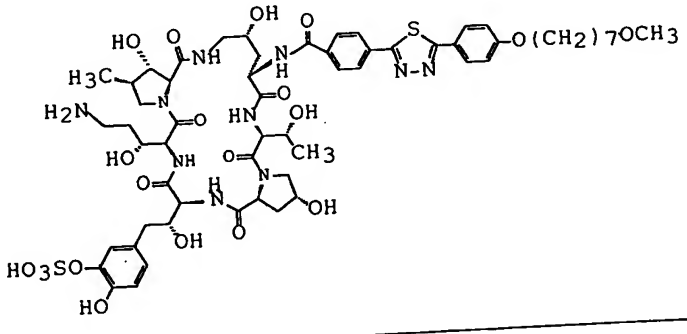
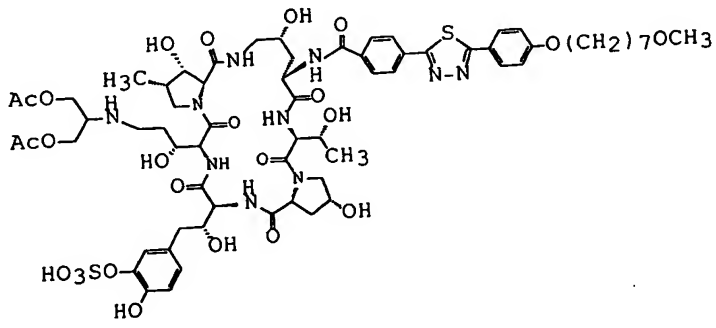
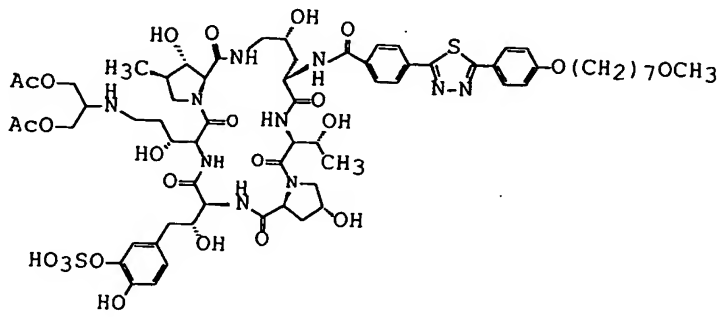
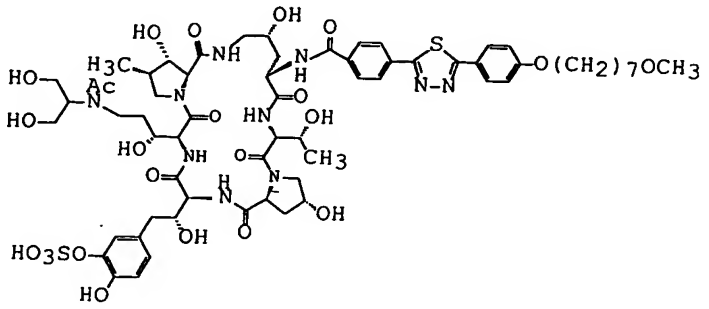
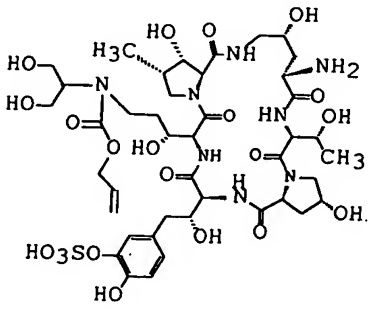
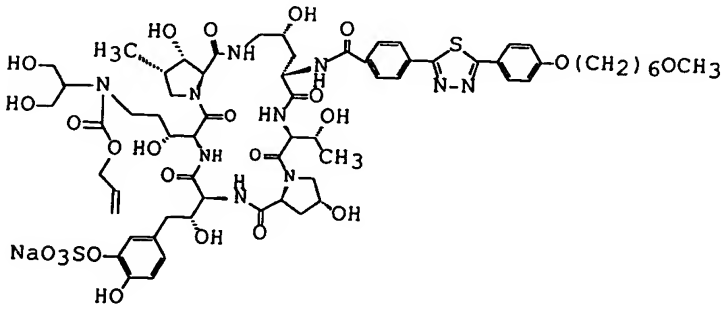
7	
	
8	
	

Example No.	Formula
9	
	
10	
	

Example No.	Formula
11	
	
12	
	

Example No.	Formula
13	
	
14	
	

Example No.	Formula
15	
	
16	
	

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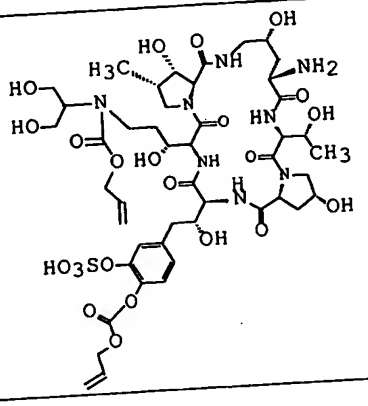
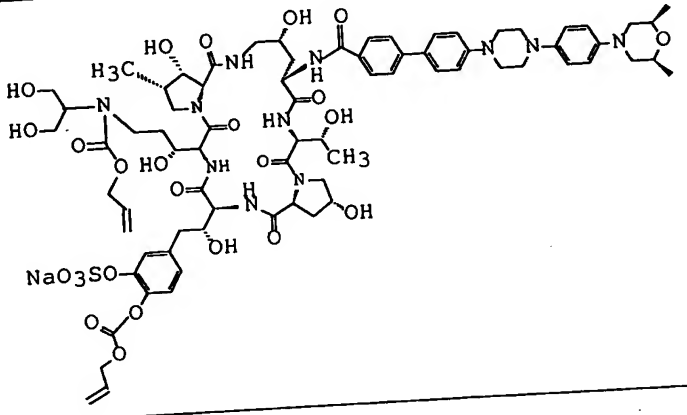
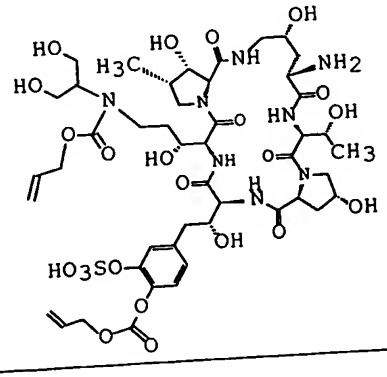
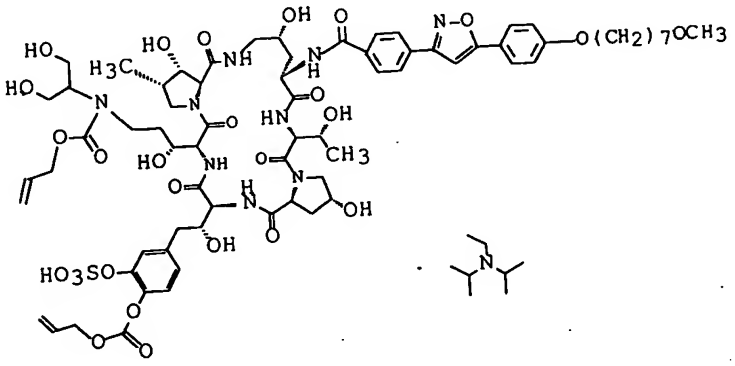
17	
	
18	
	

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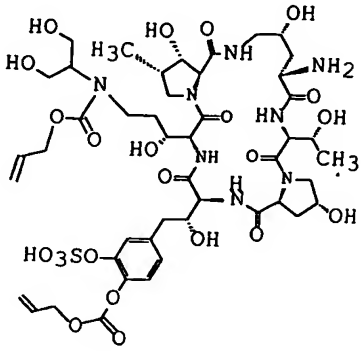
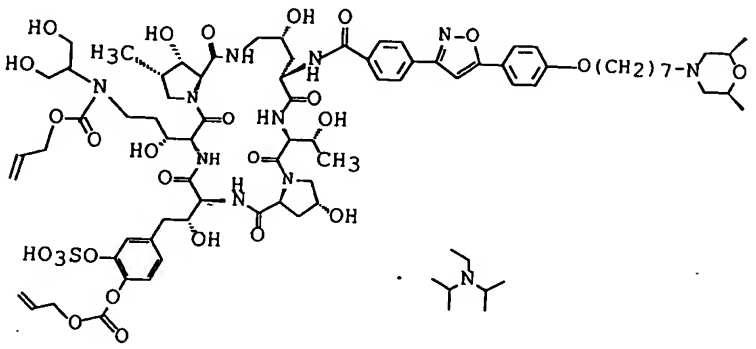
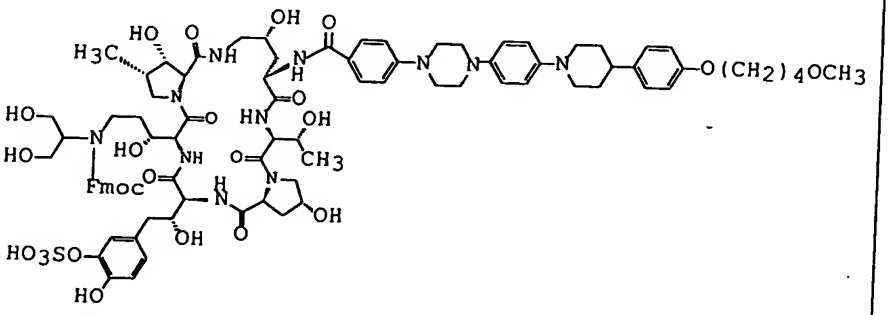
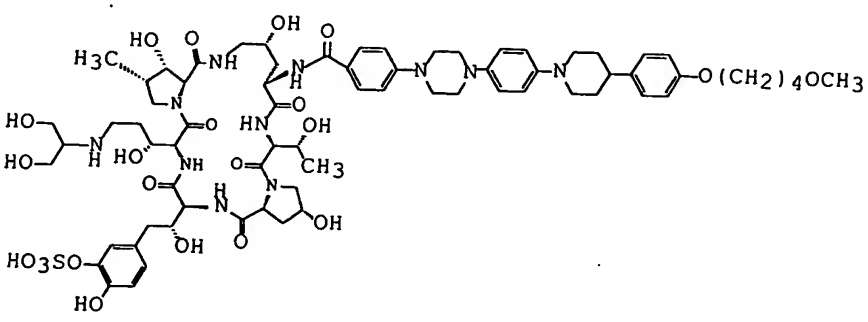
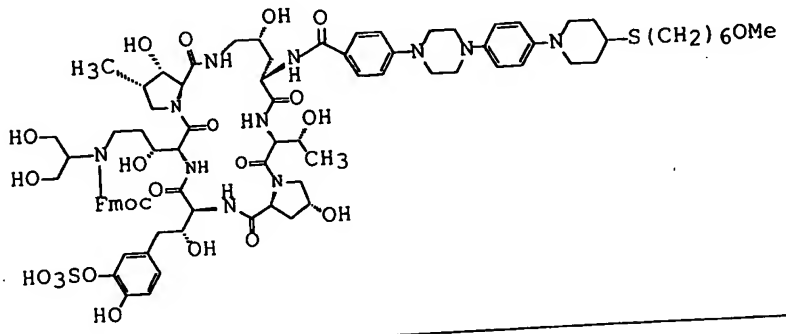
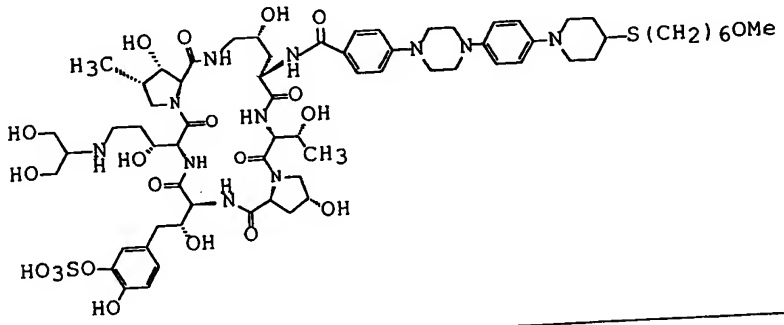
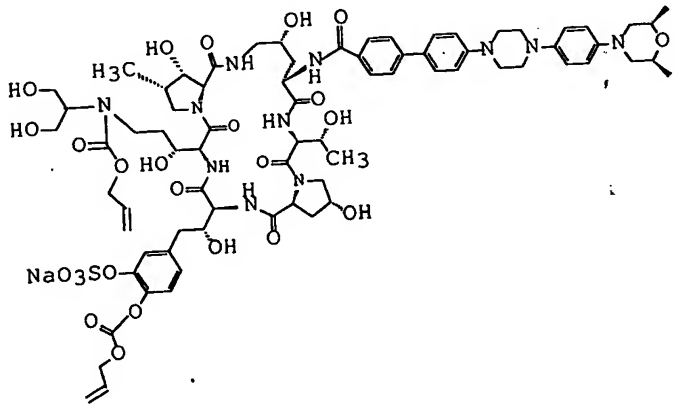
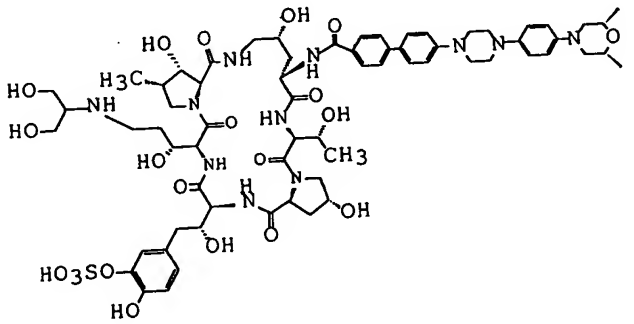
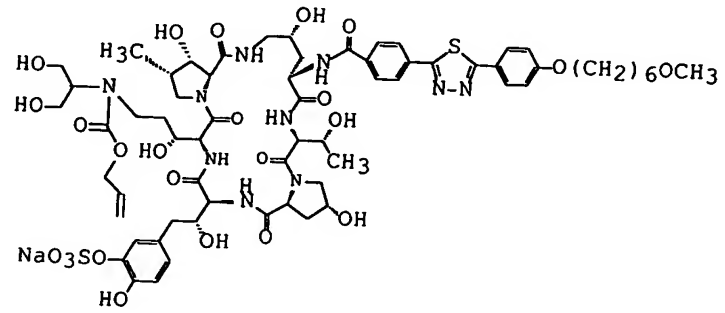
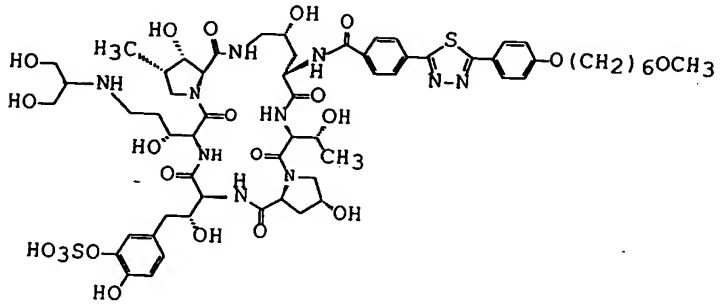
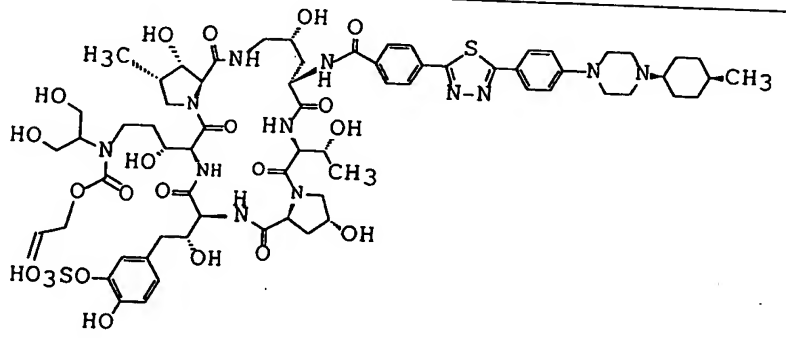
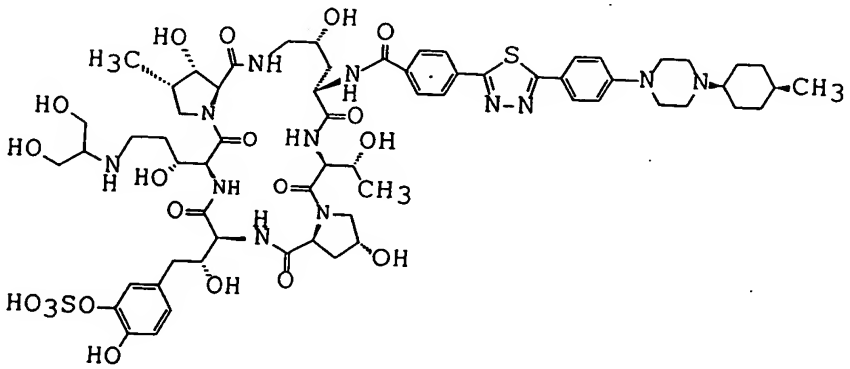
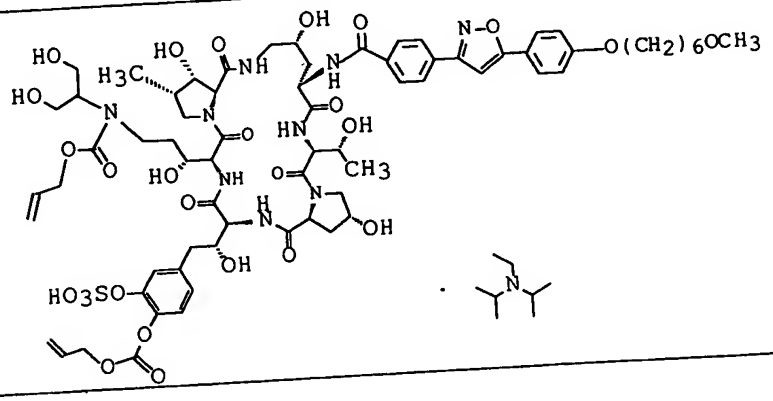
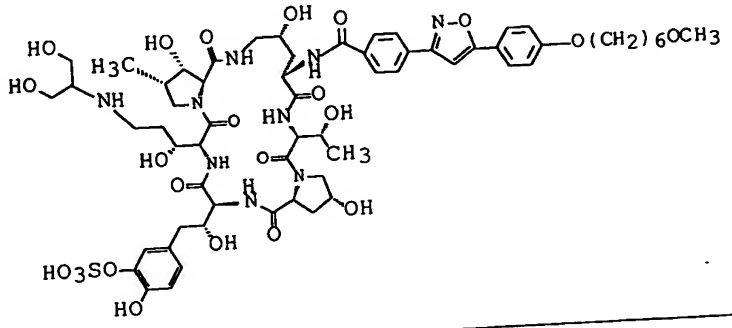
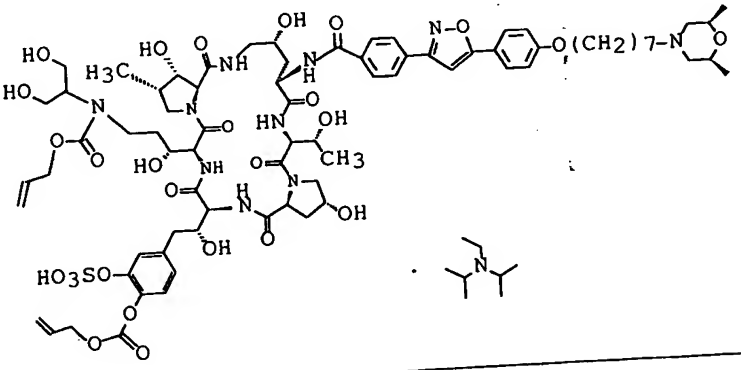
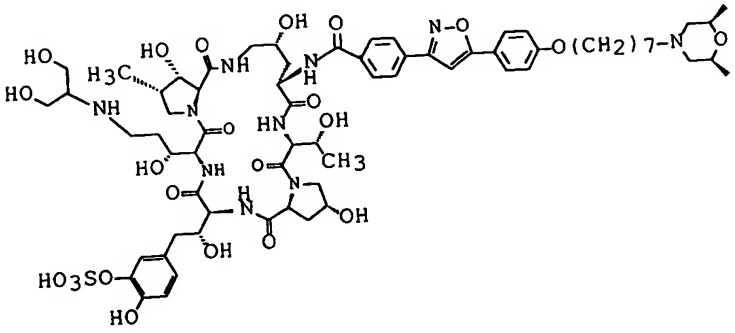
19	
	
20	
	

Example No.	Formula
21	
	
22	
	

Example No.	Formula
23	
	
24	
	

Example No.	Formula
25	
	
26	
	

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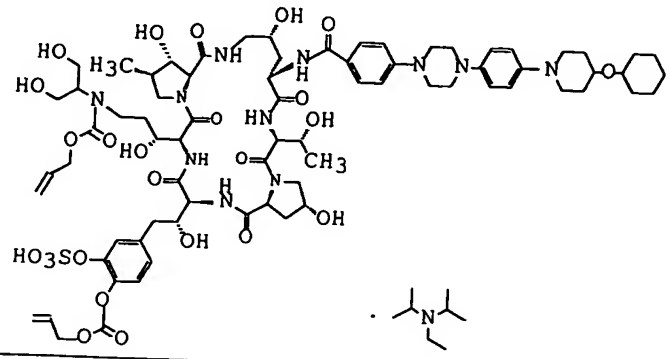
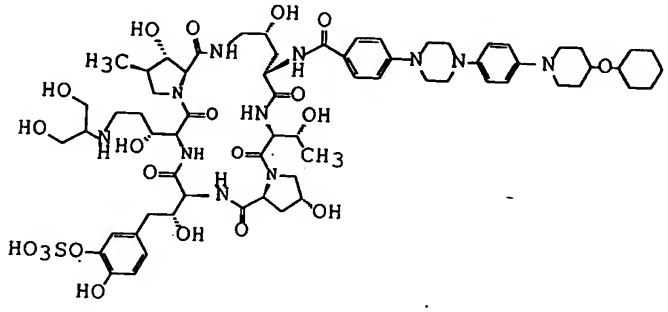
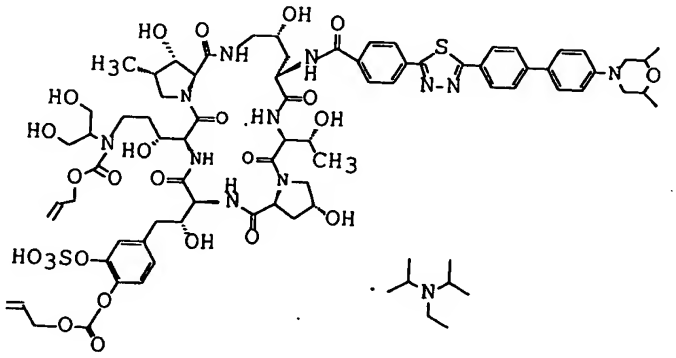
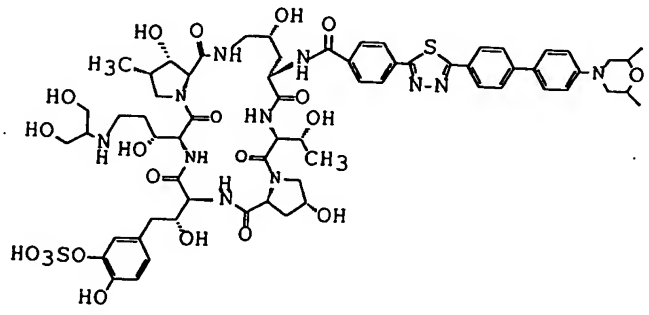
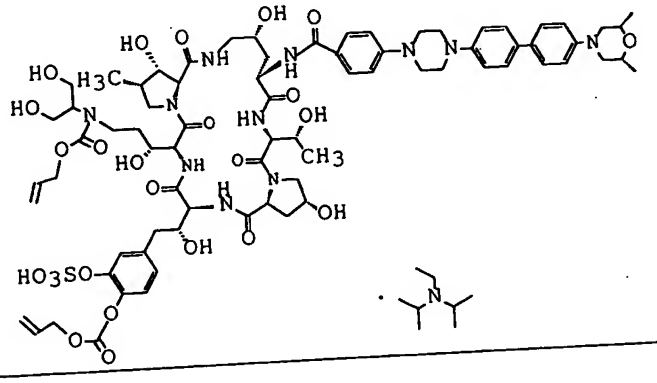
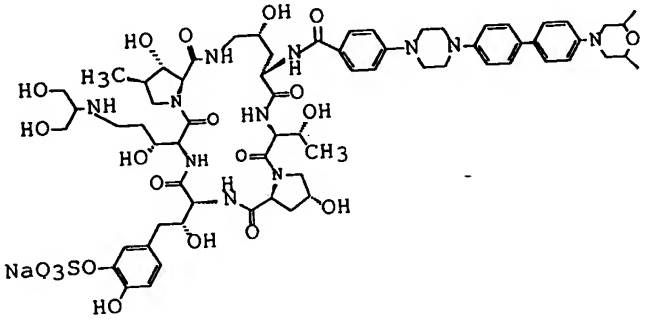
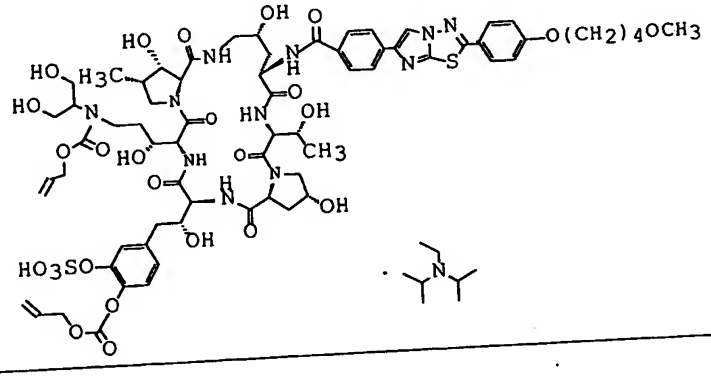
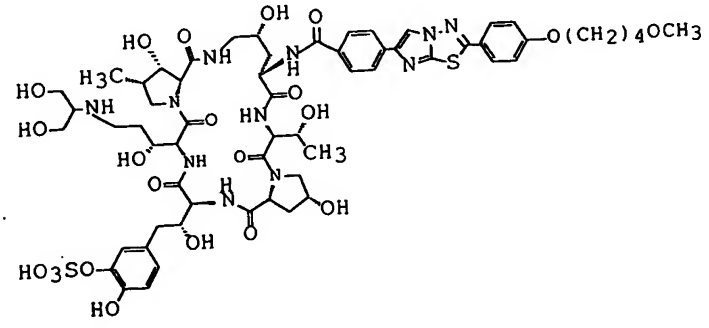
27	
	
28	
	

Example No.	Formula
29	
	
30	
	

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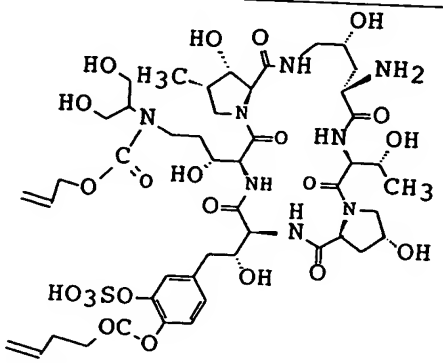
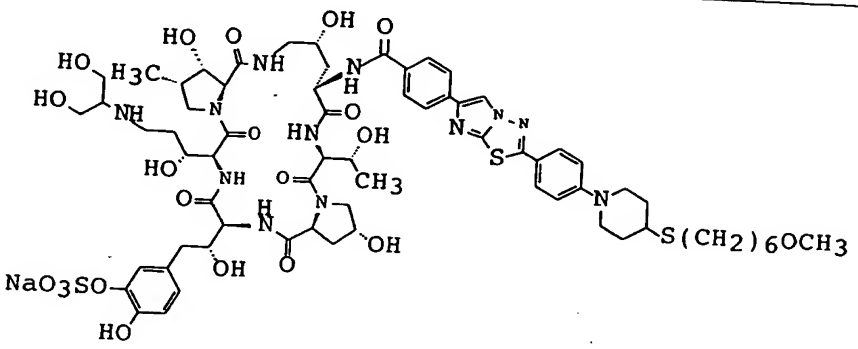
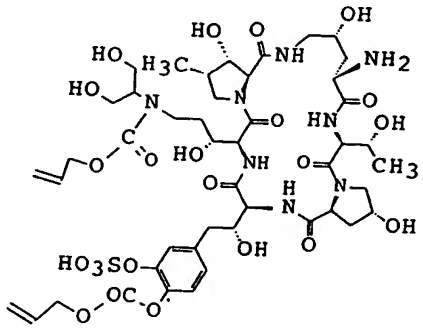
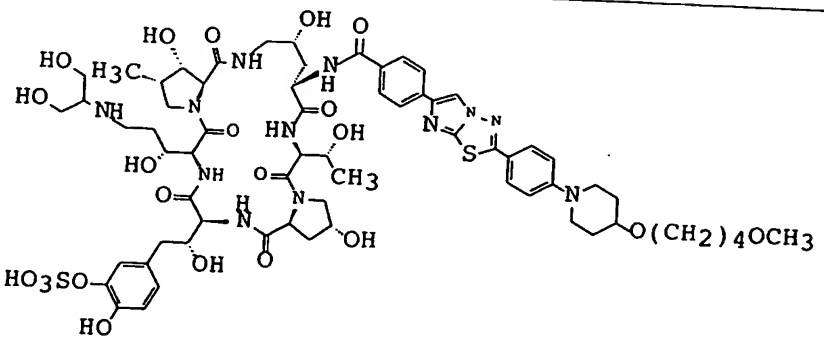
31	
	
32	
	

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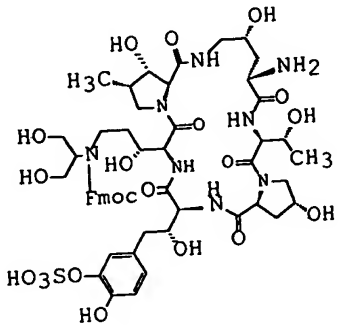
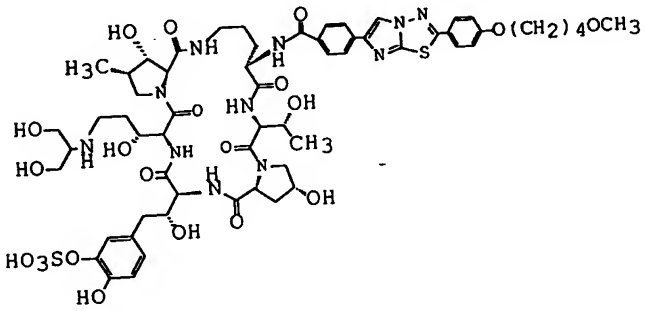
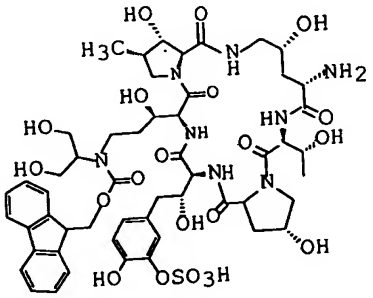
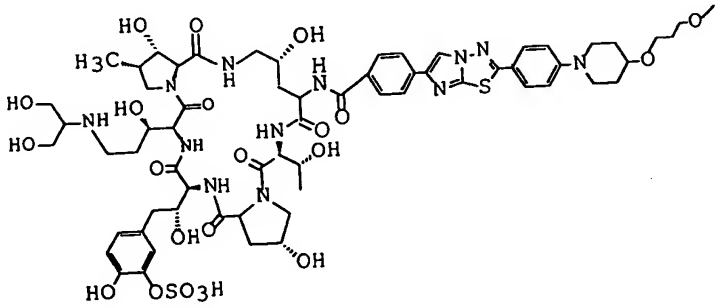
33	
	
34	
	

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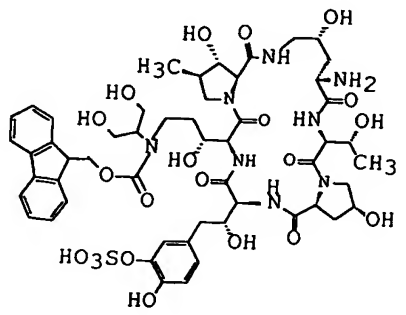
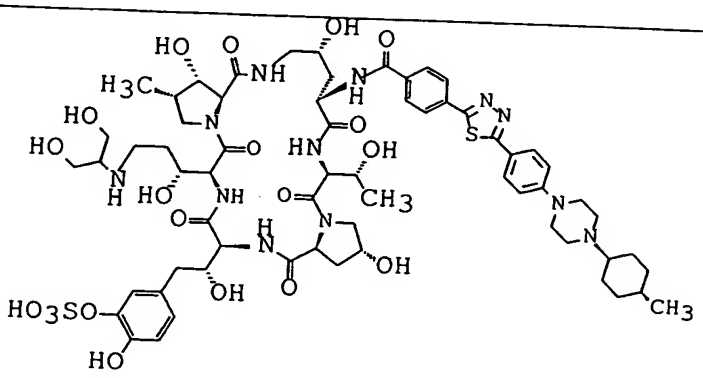
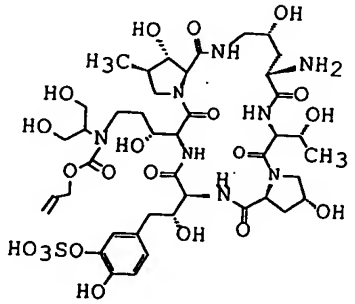
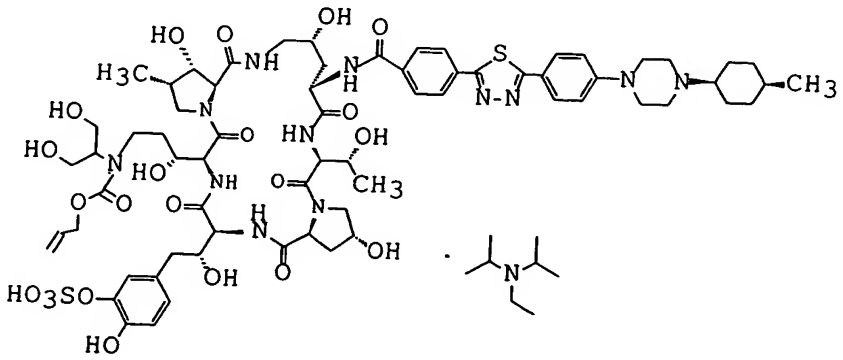
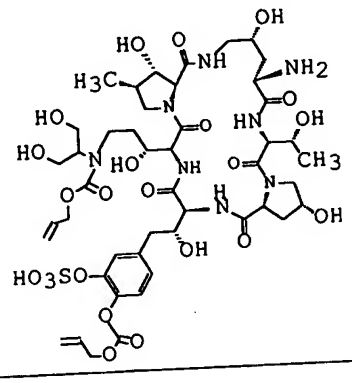
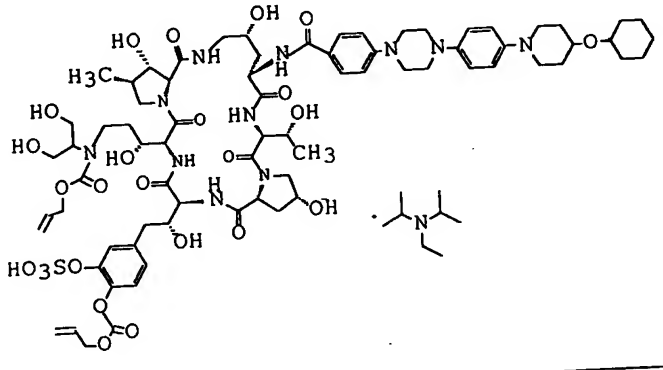
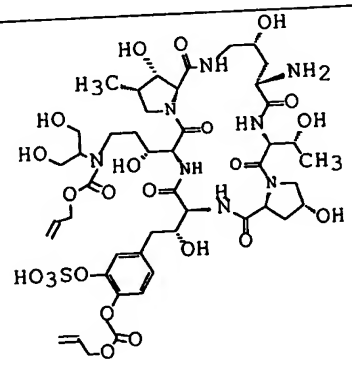
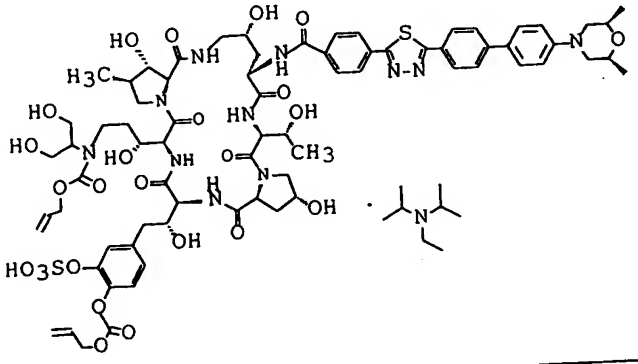
35	
	
36	
	

Example No.	Formula
37	
	
38	
	

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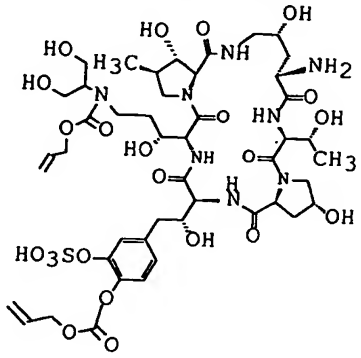
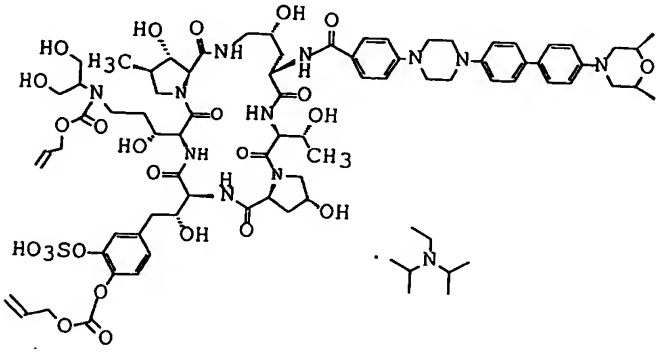
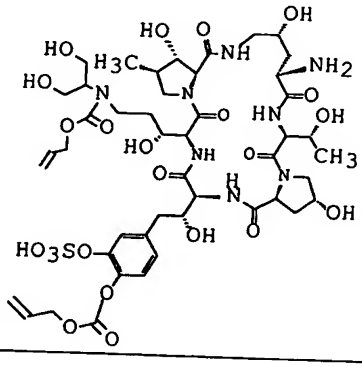
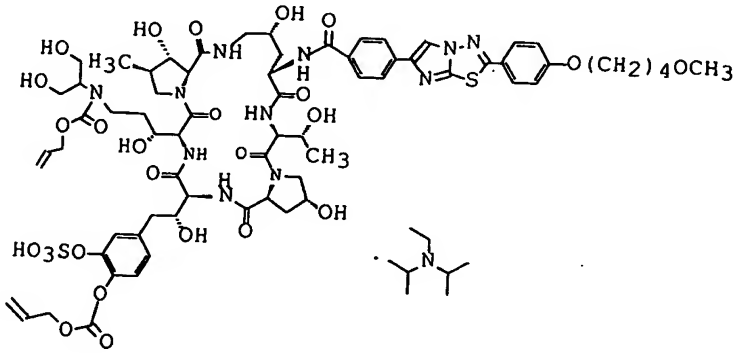
39	
	
40	
	

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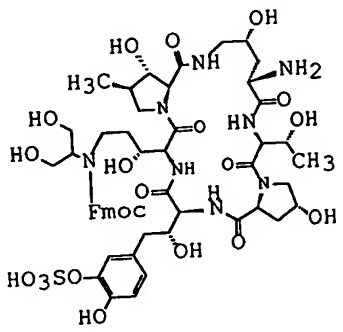
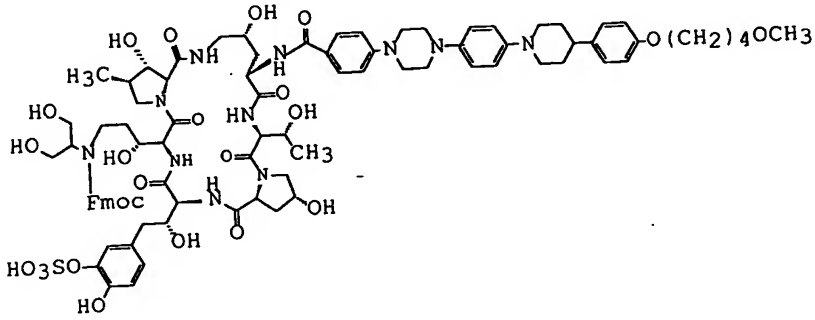
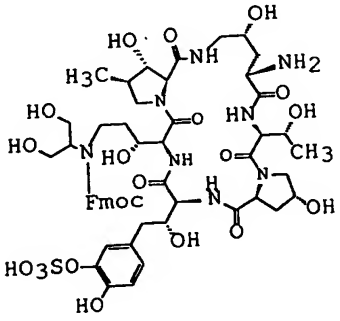
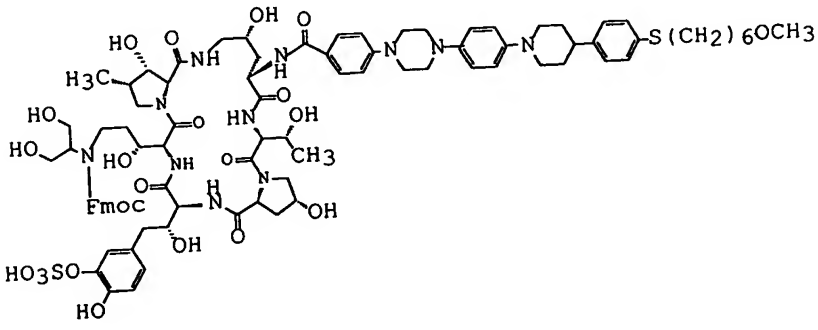
41	
	
42	
	

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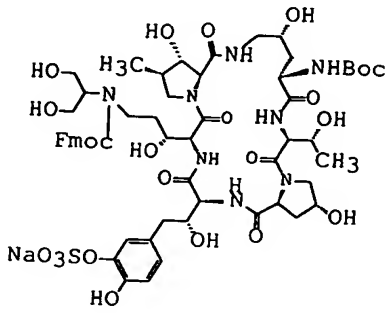
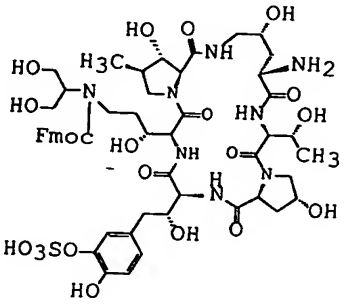
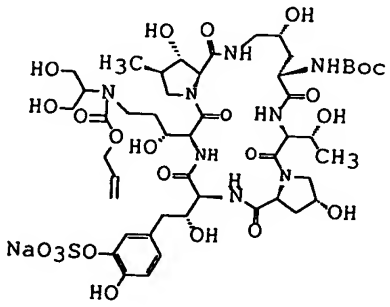
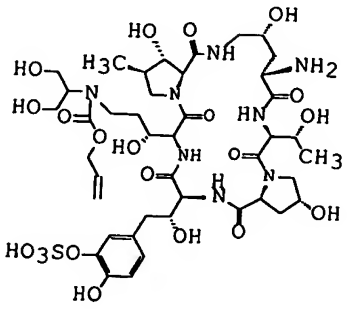
43	
	
44	
	

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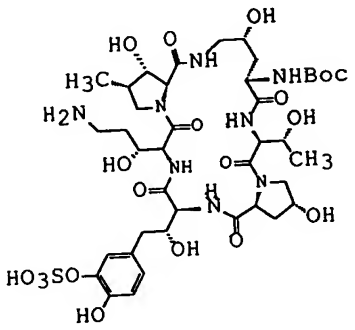
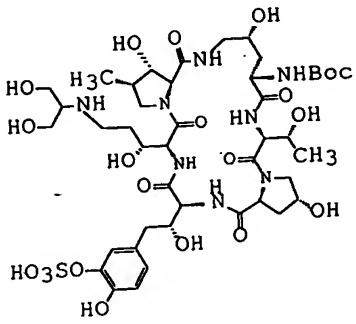
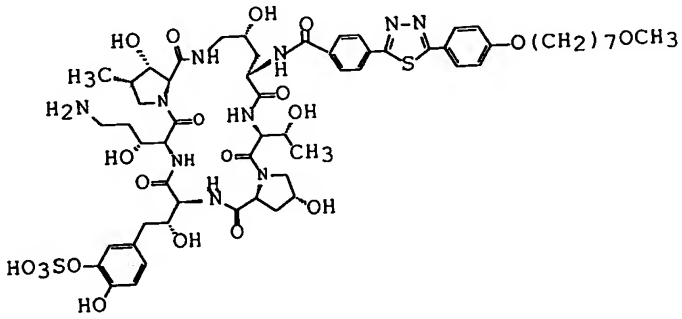
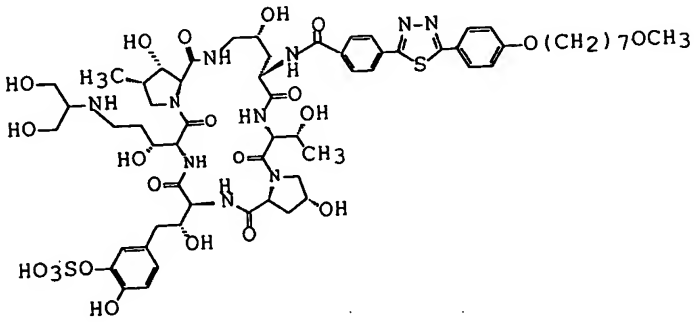
45	
	
46	
	

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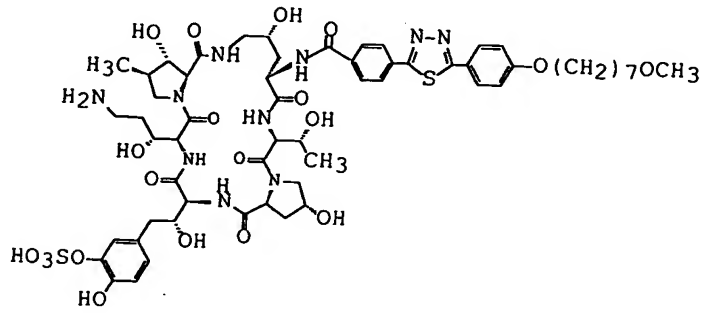
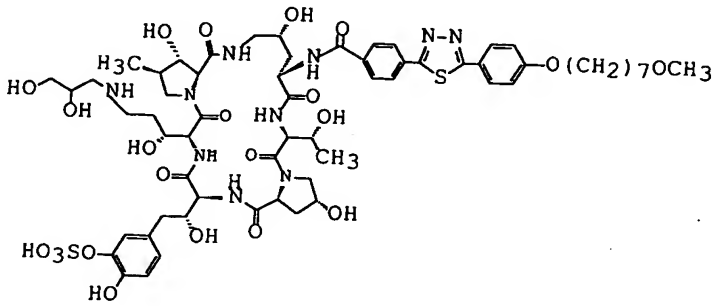
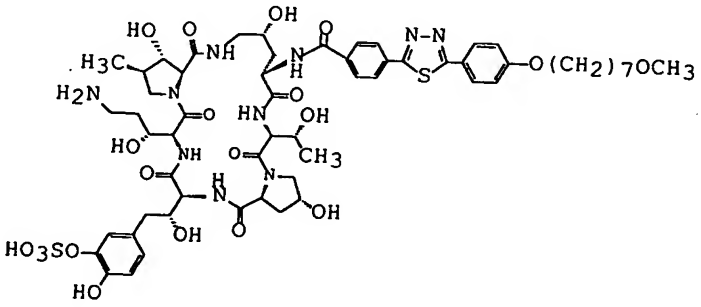
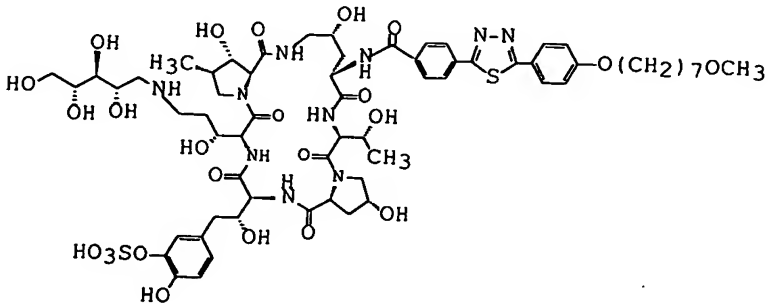
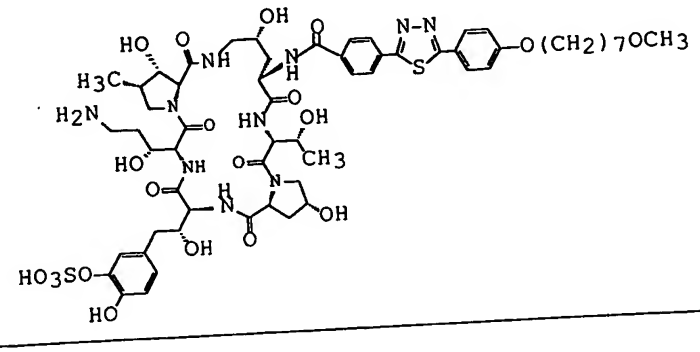
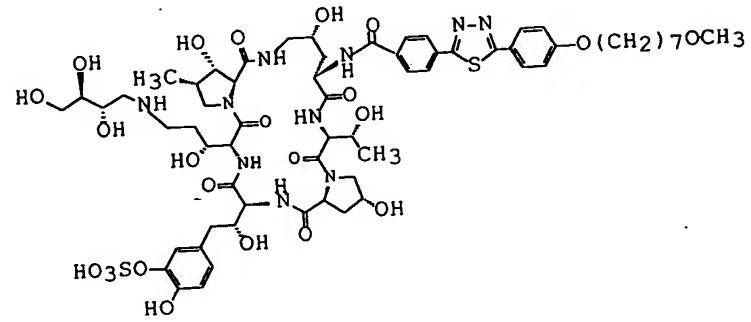
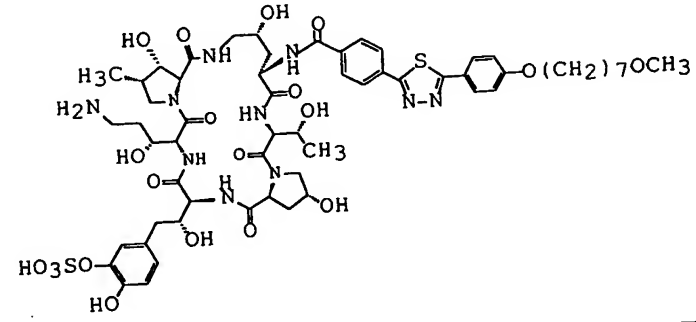
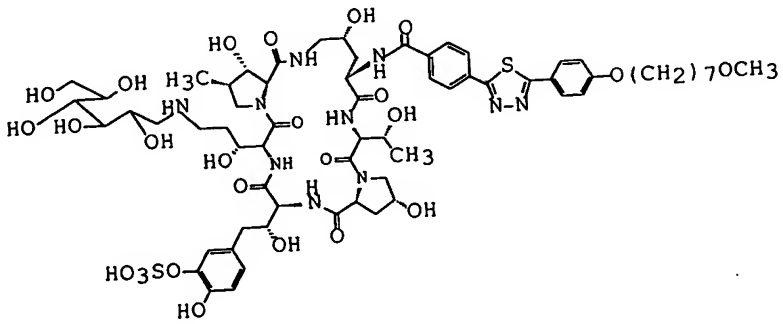
47	
	
48	
	

Example No.	Formula
49	
	
50	
	

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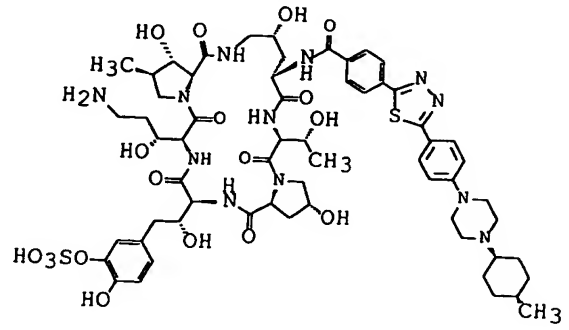
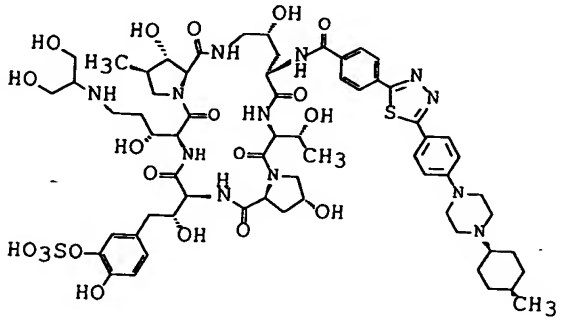
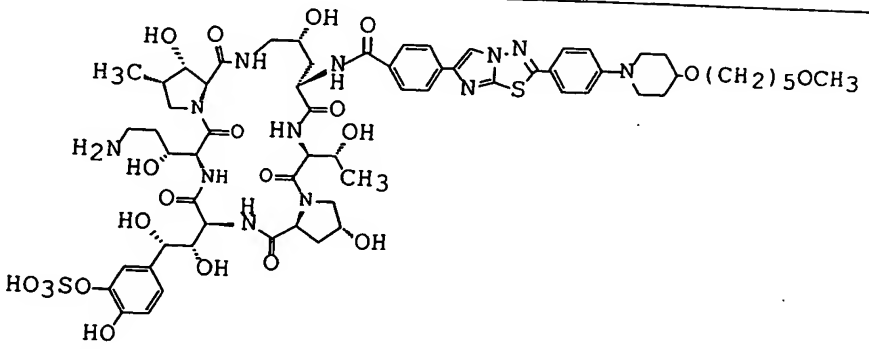
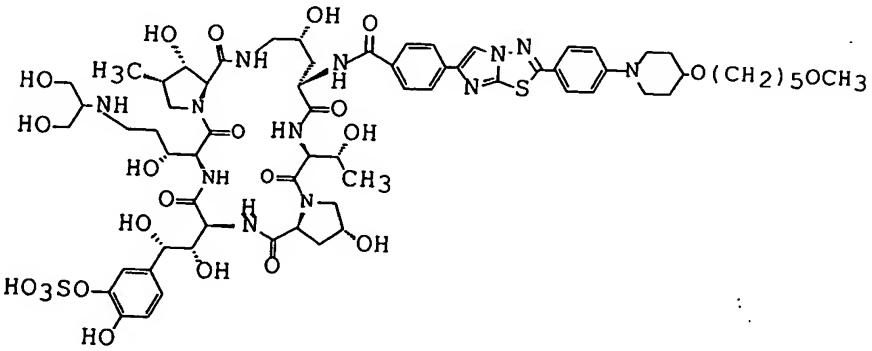
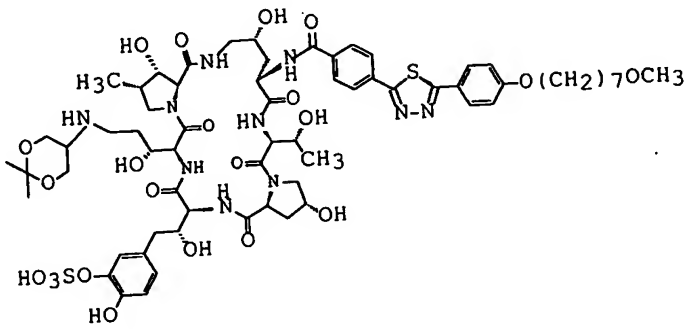
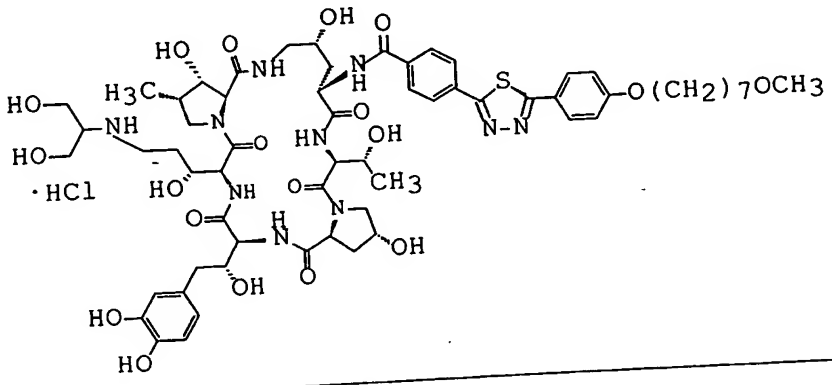
51	
	
52	
	

Example No.	Formula
53	
	

Example 1

A solution of the starting compound (1) (4.42 g) and 10% palladium on carbon (50% including water) (3.0 g) in a mixture of methanol (90 ml) and water (80 ml) was hydrogenated under an atmospheric pressure of hydrogen with stirring at ambient temperature for 8 hours. To the reaction mixture was added 10% palladium hydroxide on carbon (50% including water) (4.0 g), and the mixture was hydrogenated under an atmospheric pressure of hydrogen with stirring at ambient temperature for 16 hours. The catalyst was filtered off and washed with a mixture of methanol and water (1:1 v/v) (50 ml), and the filtrate and washes were combined. To the solution was dropwise added allyloxycarbonyl chloride (1.72 ml) in tetrahydrofuran (4 ml) adjusting pH to 8.5-10.0 with 1N sodium hydroxide with stirring on an ice-bath.

The mixture was stirred at the same temperature for 2 hours and adjusted pH to 8.0 with 1N hydrochloric acid. The solution was subjected to column chromatography on ODS (Daiso-gel, SP-120-40/60-ODS-B (Trademark: prepared by Daiso Co., Ltd.)) (400 ml) eluting with 10% acetonitrile in water and then with 20% acetonitrile in water. The first fractions containing the object compound were collected and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give the major object compound (1) (0.47 g). The second fractions containing the object compound were collected and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give the minor object compound (1) (2.91 g).

major object compound (1)

IR (KBr): 1761, 1672, 1635, 1512, 1450 cm^{-1}

NMR (DMSO-d_6 + D_2O, δ): 0.96 (3H, d, J=6.79Hz), 1.00-1.15 (3H, m), 1.35 (9H, s), 1.45-2.50 (9H, m), 2.80-3.40 (6H, m), 3.70-4.60 (16H, m), 4.65-4.90 (4H, m), 5.10-5.45 (4H, m), 5.80-6.10 (2H, m), 6.71 (1H, d, J=8.23Hz), 6.77 (1H, d, J=9.01Hz), 6.98 (1H, s)

ESI MASS (m/z)(Positive): 1277.2 (M^++Na)

minor object compound (1)

NMR (DMSO-d_6 + D_2O, δ): 0.96 (3H, d, J=6.57Hz), 1.06 (3H, d, J=4.94Hz), 1.36 (9H, s), 1.45-2.45 (8H, m), 2.75-3.70 (9H, m), 3.75-4.60 (12H, m), 4.69 (2H, d, J=5.19Hz), 4.70-4.90 (2H, m), 5.05-5.50 (3H, m), 5.80-6.10 (1H, m), 6.91 (1H, d, J=8.29Hz), 7.10 (1H, d, J=8.31Hz), 7.43 (1H, s)

ESI MASS (m/z)(Positive): 1193.3 (M^++Na)

Example 2

A suspension of the object compound (2) (1.73 g) in dichloromethane (40 ml) was stirred with cooling at 5°C and treated with triethylsilane (1.1 ml), followed by

trifluoroacetic acid (3.19 ml) dropwise over 30 minutes. After warming to room temperature, the clear solution was stirred for 2 hours, and then poured into a mixture of saturated aqueous sodium hydrogen carbonate (100 ml) and pH 6.86 standard buffer (100 ml). Organic solvent was removed by evaporation, and the remaining aqueous solution purified by ODS (Daiso-gel, SP-120-40/60-ODS-B (Trademark: prepared by Daiso Co., Ltd.)) (200 ml) column chromatography, eluting with aqueous acetonitrile (10-20%). The fractions containing the object compound were collected and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give the object compound (2) (1.10 g).

IR (KBr): 1761, 1668, 1647, 1539, 1512, 1437 cm^{-1}

NMR (DMSO-d_6 + D_2O, δ): 0.95 (3H, d, J=6.77Hz), 1.18 (3H, d, J=4.94Hz), 1.40-2.40 (7H, m), 2.70-3.40 (4H, m), 3.60-4.60 (17H, m), 4.69 (2H, d, J=5.37Hz), 4.70-4.90 (2H, m), 5.10-5.50 (4H, m), 5.80-6.20 (2H, m), 6.89 (1H, d), 7.08 (1H, d, J=8.21Hz)

ESI MASS (m/z)(Positive): 1155.4 (M^++Na)

Elemental Analysis Calcd. for $C_{46}H_{68}N_8O_{23}S \cdot 4H_2O$:

C 45.84, H 6.36, N 9.30

Found : C 45.85, H 6.33, N 9.16

Example 3

A solution of the starting compound (3) (0.43 g) in dimethylformamide (4 ml) was treated with 4-[2-[4-[4-(5-methoxypentyloxy)piperidin-1-yl]phenyl]imidazo[2,1-b][1,3,4]-thiadiazol-6-yl]benzoic acid benzotirazol-1-yl ester (194 mg) and diisopropylethylamine (78.4 µl) and stirred for 5 hours at room temperature. Ethyl acetate (50 ml) was added, and the resulting precipitate collected, washed with isopropyl ether, and dried to give the object compound (3) (610.6 mg) as a crude powder, that was used directly in the next reaction without purification.

Example 4

To a solution of the starting compound (4) (610.6 mg) in a mixture of methanol (10 ml) and tetrahydrofuran (25 ml) were successively added triphenylphosphine (32 mg), tetrakis(triphenylphosphine)palladium(0) (35 mg) and morpholine (106 µl) with stirring, and the mixture was stirred at ambient temperature for 3.5 hours. Ethyl acetate (100 ml) was added, and the resulting precipitate collected, washed with isopropyl ether, and dried to give a crude pale yellow powder (535 mg). The crude powder was dissolved sodium hydroxide aqueous solution and subjected to column chromatography on ODS (YMC-gel ODS-AM-S-50 (Trademark: prepared by YMC Co., Ltd.)) (37% acetonitrile aqueous solution). The fractions containing the object compound were combined, and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give the object compound (4) (293.7 mg).

IR (KBr): 3355.5, 1633.4, 1608.3, 1529.3, 1517.7, 1463.7, 1444.4, 1267.0, 1230.4 cm^{-1}

NMR (DMSO-d_6, δ): 0.98 (3H, d, J=6.7Hz), 1.10 (3H, d, J=5.6Hz), 1.2-5.6 (65H, m), 6.71 (1H, d, J=8.1Hz), 6.78 (1H, d, J=9.7Hz), 7.00 (1H, s), 7.09 (2H, d, J=9.1Hz), 7.75 (2H, d, J=8.7Hz), 7.95 (4H, s), 7.3-8.7 (7H, m), 8.79 (1H, s)

MASS (m/z): 1465.5 $(M-H)^-$

Elemental Analysis Calcd. for $C_{66}H_{90}N_{12}O_{22}S_2 \cdot 7H_2O$:
C 49.74, H 6.58, N 10.55
Found : C 49.72, H 6.43, N 10.40

Example 5

A solution of the starting compound (5) (10 g) in a mixture of methanol (500 ml) and water (100 ml) was treated with cobalt (II) chloride hexahydrate (9.43 g) and then stirred to give a pink solution. Sodium borohydride (7.5 g) was then added portionwise and stirred for 1 hour at ambient temperature. The reaction mixture was filtered through a bed of celite, washing with a

mixture of methanol (100 ml) and water (20 ml). The ice-cooled filtrate was then treated dropwise with a solution of allyloxycarbonyl chloride (1.46 ml) in tetrahydrofuran (10 ml), keeping pH 8.0-9.5 with 1N sodium hydroxide and then stirred for 1 hour at the same temperature. The reaction mixture was evaporated in vacuo (about 200 ml) and added 1N sodium hydroxide (60 ml), and then the mixture was stayed in the refrigerator overnight. To the solution was added water (200 ml), and the mixture was purified by ODS (Daiso-gel, SP-120-40/60-ODS-B (Trademark: prepared by Daiso Co., Ltd.)) (200 ml) column chromatography, eluting with aqueous acetonitrile (5-20%). The fractions containing the object compound were collected and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give the object compound (5) (8.58 g).

IR (KBr): 1670, 1633, 1516, 1443, 1269 cm^{-1}

NMR (DMSO-d_6 + D_2O, δ): 0.97 (3H, d, J=6.75Hz), 1.08 (3H, d, J=5.52Hz), 1.35 (9H, s), 1.40-2.00 (6H, m), 2.10-2.50 (3H, m), 2.80-3.40 (4H, m), 3.65-4.50 (14H, m), 4.65-4.85 (2H, m), 5.05-5.35 (2H, m), 5.70-6.00 (1H, m), 6.72 (1H, d, J=8.12Hz), 6.78 (1H, d, J=10.1Hz)

ESI MASS (m/z)(Positive): 1119.3 (M^++Na)

Elemental Analysis Calcd. for $C_{45}H_{67}N_8O_{21}SNa \cdot 5H_2O$:

C 44.52, H 6.37, N 9.44

Found : C 44.59, H 6.43, N 9.47

Example 6

A suspension of the starting compound (6) (8.5 g) in dichloromethane (180 ml) was stirred with cooling at 5°C and treated with triethylsilane (6.2 ml), followed by trifluoroacetic acid (17.9 ml) dropwise over 30 minutes. After warming to room temperature, the clear solution was stirred for 2 hours, then poured into a mixture of saturated aqueous sodium hydrogen carbonate (200 ml) and pH 6.86 standard buffer (200 ml). Organic solvent was removed by evaporation, and the remaining aqueous solution purified by ODS (Daiso-gel, SP-120-40/60-ODS-B

(Trademark: prepared by Daiso Co., Ltd.)) (200 ml) column chromatography, eluting with aqueous acetonitrile (5-20%). The fractions containing the object compound were collected and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give the object compound (6) (5.53 g).

NMR (DMSO-d_6 + D_2O, δ): 0.97 (3H, d, J=6.64Hz), 1.15 (3H, d, J=5.52Hz), 1.30-1.70 (3H, m), 1.80-2.50 (6H, m), 2.70-4.00 (14H, m), 4.20-4.60 (8H, m), 4.70-4.90 (2H, m), 5.10-5.40 (2H, m), 5.70-6.10 (1H, m), 6.70-6.90 (2H, m), 7.06 (1H, s)

ESI MASS (m/z)(Positive): 997.3 (M^++Na)

Example 7

A solution of the starting compound (7) (0.5 g) in dimethylformamide (10 ml) was treated with 4-[5-[4-[4-(cis-4-methylcyclohexyl)piperazinyl]phenyl]-1,3,4-thiadiazol-2-yl]benzoic acid benzotriazol-1-yl ester (0.3 g) and diisopropylethylamine (0.13 ml) and stirred for 20 hours at room temperature. Ethyl acetate (100 ml) was added and the resulting precipitate collected, washed with ethyl acetate, and dried to give the object compound (7) (0.5 g).

NMR (DMSO-d_6, δ): 0.90 (3H, d, J=6.8Hz), 0.97 (3H, d, J=6.6Hz), 1.13 (3H, d, J=5.0Hz), 1.43-6.10 (78H, m), 6.69-8.72 (18H, m)

ESI MASS (m/z)(Negative): 1418.4 (M^+)

Example 8

To a suspension of the starting compound (8) (0.38 g) in a mixture of methanol (7.6 ml) and tetrahydrofuran (1.9 ml) were successively added triphenylphosphine (0.04 g), tetrakis(triphenylphosphine)palladium(0) (0.088 g) and morpholine (0.14 ml) with stirring and the mixture was stirred at ambient temperature for 15 hours. To the reaction mixture was added ethyl acetate (100 ml). The resulting precipitate was collected by filtration and dried in vacuo. The precipitate was

dissolved in a mixture of water and 1N sodium hydroxide and the solution was subjected to column chromatography on ODS (Daiso-gel, SP-120-40/60-ODS-B (Trademark: prepared by Daiso Co., Ltd.)) (100 ml) eluting with 40% acetonitrile in water. The fractions containing the object compound were collected and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give the object compound (8) (0.25 g).

NMR (DMSO-d_6, δ): 0.90 (3H, d, J=6.7Hz), 0.98 (3H, d, J=6.7Hz), 1.11 (3H, d, J=5.7Hz), 1.42-5.23 (56H, m), 6.69-8.92 (17H, m)

ESI MASS (m/z)(Negative): 1334.4 (M^+)

Elemental Analysis Calcd. for $C_{61}H_{82}N_{12}O_{18}S_2 \cdot 8H_2O$:
C 49.52, H 6.68, N 11.36

Found : C 49.25, H 6.41, N 11.20

Example 9

The suspension of a mixture of the starting compound (9) (100 mg), 1,3-dihydroxyacetate (13.5 mg) and acetic acid (0.13 ml) in a mixture of methanol (1.5 ml) and dimethylformamide (0.7 ml) was added sodium cyanoborohydride (9.4 mg) with stirring at ambient temperature, and the mixture was stirred at the same temperature overnight. To the reaction mixture was added ethyl acetate (20 ml). The resulting precipitate was collected by filtration and dried in vacuo. The precipitate was dissolved in a mixture of water and 1N sodium hydroxide and the solution was subjected to column chromatography on ODS (Daiso-gel, SP-120-40/60-ODS-B (Trademark: prepared by Daiso Co., Ltd.)) (50 ml) eluting with 40% acetonitrile in water. The fractions containing the object compound were collected and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give the object compound (9) (55 mg).

NMR (DMSO-d_6, δ): 0.90 (3H, d, J=6.8Hz), 0.98 (3H, d, J=6.7Hz), 1.11 (3H, d, J=5.5Hz), 1.43-5.24 (62H, m), 6.69-8.85 (17H, m)

ESI MASS (m/z)(Negative): 1408.3(M^+)

Example 10

To a solution of a mixture of the starting compound (10) (7.5 g), 1,3-dihydroxyacetone (1.19 g) and acetic acid (1.14 ml) in a mixture of methanol (120 ml) and dimethylformamide (55 ml) was added sodium cyanoborohydride (835 mg) with stirring at ambient temperature, and the mixture was stirred at the same temperature overnight. To a reaction mixture was poured into ethyl acetate (700 ml). The resulting precipitates were collected by filtration, washed with ethyl acetate (100 ml) and dried in vacuo. The precipitates were dissolved in a mixture of 30% aqueous acetonitrile (800 ml) and 1N sodium hydroxide (5 ml). The solution was subjected to column chromatography on ODS (Daiso-gel, SP-120-40/60-ODS-B (Trademark: prepared by Daiso Co., Ltd.)) (440 ml) eluting in turn with water and aqueous acetonitrile (30%-60%). The fractions containing the object compound were collected and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give the object compound (10) (5.22 g).

IR (KBr): 1632, 1535, 1518, 1443, 1269, 1082, 1047 cm^{-1}

NMR (DMSO-d_6 + D_2O, δ): 0.82 (3H, d, J=6.83Hz),0.97 (3H, d, J=6.81Hz), 1.02 (3H, d, J=6.18Hz), 1.24 (26H, s), 1.35-2.45 (14H, m), 2.75-3.40 (5H, m), 3.60-4.50 (15H, m), 4.7-4.90 (2H, m), 6.65-6.80 (2H, m), 7.01 (1H, s)

ESI MASS (m/z)(Positive): 1088.4 (M^++Na)

Example 11

To a solution of the starting compound (11) (4.0 g) in dimethylformamide (40 ml) were successively added diisopropylethylamine (1.45 ml) and 9-fluorenylmethyl chloroformate (1.03 g), and the mixture was stirred at ambient temperature for 2 hours. The reaction mixture was poured into water (200 ml). The solution was purified by ODS (Daiso-gel, SP-120-40/60-ODS-B (Trademark: prepared by Daiso Co., Ltd.)) (200 ml) column chromatography, eluting in turn with a mixture

of saturated aqueous sodium chloride (400 ml), saturated aqueous sodium hydrogen carbonate (50 ml) and water (400 ml), and aqueous acetonitrile (30-60%). The fractions containing the object compound were collected and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give the object compound (11) (2.82 g).

IR (KBr): 1666, 1632, 1518, 1446, 1273, 1246, 1082, 1047 cm^{-1}

NMR (DMSO-d_6 + D_2O, δ): 0.80-1.10 (9H, m), 1.23 (26H, s), 1.35-2.45 (12H, m), 2.60-3.40 (6H, m), 3.60-4.55 (18H, m), 4.65-4.90 (2H, m), 6.65-6.85 (2H, m), 6.97 (1H, s), 7.30-7.50 (4H, m), 7.60-7.95 (4H, m)

ESI MASS (m/z)(Negative): 1423.7 (M^+-Na)

Elemental Analysis Calcd. for $C_{69}H_{99}N_8O_{22}SNa \cdot 6H_2O$:
C 53.27, H 7.19, N 7.20
Found : C 53.45, H 7.21, N 7.10

Example 12

To a solution of the object compound (12) (1.21 g) in dimethylformamide (15 ml) were successively added diisopropylethylamine (0.26 ml) and di-tert-butyl dicarbonate (285 mg), and the mixture was stirred at ambient temperature overnight. The reaction mixture was poured into a mixture of pH 6.86 standard buffer solution (150 ml), saturated aqueous sodium chloride (50 ml) and saturated aqueous sodium hydrogen carbonate (20 ml). The mixture was purified by ODS (Daiso-gel, SP-120-40/60-ODS-B (Trademark: prepared by Daiso Co., Ltd.)) (200 ml) column chromatography, eluting with aqueous acetonitrile (30-50%). The fractions containing the object compound were collected and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give the object compound (12) (1.19 g).

IR (KBr): 1662, 1632, 1535, 1518, 1444, 1367, 1272, 1250 cm^{-1}

NMR (DMSO-d_6 + D_2O, δ): 0.85 (3H, d, J=6.76Hz), 0.96 (3H, d,

J=6.77Hz), 1.04 (3H, d, J=5.50Hz), 1.23 (26H, s), 1.37 (9H, s), 1.40-1.50 (2H, m), 1.55-2.50 (10H, m), 2.80-3.40 (6H, m), 3.50-4.45 (14H, m), 6.65-6.80 (2H, m), 6.96 (1H, s)

ESI MASS (m/z)(Negative): 1301.6 (M^+-Na)

Example 13

To a solution of a mixture of starting compound (13) (1.62 g) and diisopropylethylamine (0.58 ml) in DMF (16 ml) was added 9-fluorenylmethyloxycarbonyl chloride (493 mg) with stirring at ambient temperature, and the mixture was stirred at the same temperature for 3 hours. The reaction mixture was poured into ethyl acetate (250 ml). To the mixtures was added pH 6.86 standard buffer solution (100 ml) and 5% aqueous sodium chloride (20 ml), and the aqueous layer was separated. The organic layer was extracted with 5% aqueous sodium chloride (100 ml), and these aqueous layers were collected and evaporated in vacuo to remove organic solvent. The solution was subjected to column chromatography on ODS (Daiso-gel, SP-120-40/60-ODS-B (Trademark: prepared by Daiso Co., Ltd.)) (200 ml) eluting with 40% acetonitrile in water. The fractions containing the object compound were collected and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give object compound (13) (1.38 g).

NMR (DMSO-d_6 + D_2O, δ): 0.89 (3H, d, J=6.26Hz), 1.09 (3H, broad s), 1.33 (9H, s), 1.40-2.10 (5H, m), 2.10-2.35 (2H, m), 2.75-3.40 (5H, m), 3.50-4.50 (16H, m), 4.60-4.90 (2H, m), 6.65-6.80 (2H, m), 6.97 (1H, s), 7.25-7.50 (4H, m), 7.70 (2H, d, J=6.82Hz), 7.88 (2H, d, J=6.77Hz)

ESI MASS (m/z)(Positive): 1331.3 (M^++Na)

Elemental Analysis Calcd. for $C_{58}H_{77}N_8O_{23}SNa \cdot 4H_2O$:
C 50.43, H 6.20, N 8.11
Found: C 50.14, H 6.28, N 8.12

Example 14

To a solution of a mixture of starting compound (14) (300 mg), 2-oxo-1,3-diacetoxypropane (121 mg) and acetic acid (40 µl) in a mixture of methanol (4.0 ml) and DMF (4.0 ml) was added sodium cyanoborohydride (29 mg) with stirring at ambient temperature, and the mixture was stirred at the same temperature overnight. The reaction mixture was concentrated in vacuo. To the resulting residue was added pH 6.86 standard buffer solution (10 ml) and acetonitrile (2 ml), and the solution was subjected to column chromatography on ODS (Daiso-gel, SP-120-40/60-ODS-B (Trademark: prepared by Daiso Co., Ltd.)) (80 ml) eluting with 40% acetonitrile in water. The fractions containing the object compound were collected and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give object compound (14) (60 mg).

NMR (DMSO-d_6 + D_2O, δ): 0.98 (3H, d, J=6.83Hz), 1.07 (3H, d, J=5.34Hz), 1.20-1.60 (10H, m), 1.60-1.90 (5H, m), 1.96 (3H, s), 2.01 (3H, s), 3.20 (3H, s), 3.31 (4H, t, J=6.33Hz), 3.80-4.55 (16H, m), 4.75-4.90 (2H, m), 6.65-6.80 (2H, m), 7.03 (1H, s), 7.14 (2H, d, J=8.84Hz), 7.90-8.15 (6H, m)

ESI MASS (m/z)(Negative): 1455.3 (M^+-1)

Example 15

To a solution of starting compound (15) (58 mg) in a mixture of methanol (3 ml) and water (3 ml) were added morpholine (35 µl) and saturated aqueous sodium carbonate (1 ml), and the mixture was stirred at ambient temperature for 1 hour. The reaction mixture was poured into pH 6.86 standard buffer solution (60 ml), and the solution was subjected to column chromatography on ODS (Daiso-gel, SP-120-40/60-ODS-B (Trademark: prepared by Daiso Co., Ltd.)) (50 ml) eluting with 30% acetonitrile in water. The fractions containing the object compound were collected and evaporated under reduced pressure to remove acetonitrile. The

residue was lyophilized to give object compound (15) (35 mg).

NMR (DMSO-d_6 + D_2O, δ): 0.97 (3H, d, J=6.78Hz), 1.12 (3H, broad s), 1.25-1.65 (8H, m), 1.65-2.00 (4H, m), 2.01 (3H, d, s), 3.21 (3H, s), 3.31 (4H, t, J=6.34Hz), 3.70-4.50 (14H, m), 4.85-4.90 (2H, m), 6.60-6.95 (2H, m), 7.00 (1H, s), 7.14 (2H, d, J=8.74Hz), 8.00 (2H, d, J=8.77Hz), 8.03 (2H, d, J=7.63Hz), 8.12 (2H, d, J=8.42Hz)

ESI MASS (m/z)(Negative): 1413.4 (M^+-1-Na)

Example 16

To a solution of starting compound (16) (100 mg) in DMF (3 ml) were added 4-[5-[4-(6-methoxyhexyl)phenyl][1,3,4]-thiadiazol-2-yl]benzoic acid benzotriazol-1-yl ester (71 mg) and diisopropylethylamine (23 µl) with stirring, and the mixture was stirred at ambient temperature overnight. To the reaction mixture was added ethyl acetate (30 ml). The resulting precipitates were collected by filtration, washed with ethyl acetate (10 ml) and dried in vacuo. The resulting residue was dissolved in a mixture of pH 6.86 standard buffer solution and 1N sodium hydroxide, and insoluble materials were filtered off and the solution was subjected to column chromatography on ODS (Daiso-gel, SP-120-40/60-ODS-B (Trademark: prepared by Daiso Co., Ltd.)) (50 ml) eluting with 30% acetonitrile in water. The fractions containing the object compound were collected and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give object compound (16) (86.5 mg).

NMR (DMSO-d_6 + D_2O, δ): 0.97 (3H, d, J=6.53Hz), 1.08 (3H, d, J=8.66Hz), 1.30-2.00 (14H, m), 2.80-3.10 (4H, m), 3.22 (3H, s), 3.90-4.55 (16H, m), 4.65-4.90 (2H, m), 5.10-5.40 (2H, m), 6.82 (2H, br s), 7.00 (1H, s), 7.14 (2H, d, J=9.17Hz), 7.90-8.20 (6H, m)

ESI MASS (m/z)(Negative): 1441.4 (M^+-1-Na)

Example 17

To a solution of starting compound (17) (200 mg) in N,N-dimethylformamide (DMF) (3 ml) were added 4'-[4-4-(cis-2,6-dimethylmorpholin-4-yl)phenyl]piperazin-1-yl]-1,1'-biphenyl-4-carboxylic acid benzotriazol-1-yl ester (57 mg) and diisopropylethylamine (22 µl) with stirring, and the mixture was stirred at ambient temperature overnight. To the reaction mixture was added ethyl acetate (30 ml). The resulting precipitates were collected by filtration, washed with ethyl acetate (10 ml) and dried in vacuo. The resulting residue was dissolved in a mixture of pH 6.86 standard buffer solution and 1N sodium hydroxide, and insoluble material were filtered off and the solution was subjected to column chromatography on ODS (Daiso-gel, SP-120-40/60-ODS-B (Trademark: prepared by Daiso Co., Ltd.)) (100 ml) eluting with 40% acetonitrile in water. The fractions containing the object compound were collected and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give object compound (17) (230 mg).

NMR (DMSO-d_6 + D_2O, δ): 0.97 (3H, d, J=6.82Hz), 1.14 (6H, d, J=6.16Hz), 1.25 (3H, d, J=6.34Hz), 1.30-2.40 (6H, m), 3.00-3.40 (10H, m), 3.60-4.10 (10H, m), 4.10-4.55 (6H, m), 4.60-4.80 (4H, m), 5.05-5.50 (4H, m), 5.80-6.10 (2H, m), 6.80-7.00 (4H, m), 7.08 (2H, d, J=8.10Hz), 7.11 (2H, d, J=8.88Hz), 7.42 (1H, s), 7.66 (2H, d, J=8.64Hz), 7.72 (2H, d, J=8.46Hz), 7.93 (2H, d, J=8.38Hz)

ESI MASS (m/z)(Negative): 1584.6 (M^+-Na)

Example 18

A mixture of 4-[5-[4-(6-methoxyhexyloxy)phenyl]-isoxazol-3-yl]benzoic acid (70 mg), 1-hydroxybenzotriazole (35.8 mg), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (40.6 mg) and N,N-diisopropylethylamine (46.1 µl) in N,N-dimethylformamide (2 ml) was stirred for 3 hours. To the reaction mixture was added starting compound (18) (200 mg) and the resulting mixture was stirred for 19 hours. To the reaction

mixture was added ethyl acetate (100 ml). The resulting precipitate was collected by filtration and washed with diisopropyl ether to give object compound (18) as a crude white powder (294.4 mg), that was used crude in the next reaction.

The following compound was obtained according to a similar manner to that of Example 18.

Example 19

The object compound (19) was used directly in the next reaction without purification.

Example 20

To a solution of starting compound (20) (287.9 mg) in N,N-dimethylformamide (3 ml) was added piperidine (0.17 ml) at room temperature. The solution was stirred for 1 hour at the same temperature. Ethyl acetate was added to the reaction mixture. The powder was collected by filtration to give crude material (203.8 mg). The crude material was purified by column chromatography on ODS to give object compound (20) (85.6 mg).

IR (KBr): 1632, 1512, 1446, 1230 cm^{-1}

NMR (DMSO-d_6, δ): 0.97 (3H, d, J=6.7Hz), 1.08 (3H, d, J=5.2Hz), 1.5-3.0 (23H, m), 3.0-4.5 (39H, m), 4.6-5.4 (10H, m), 6.6-7.1 (11H, m), 7.17 (2H, d, J=8.7Hz), 7.3-7.6 (2H, m), 7.81 (2H, d, J=8.6Hz), 8.0-8.5 (2H, m), 8.71 (1H, s)

MASS (m/z): 1488 (M^++1)

The following compound was obtained according to a similar manner to that of Example 20.

Example 21

IR (KBr): 1632, 1512, 1444, 1232 cm^{-1}

NMR (DMSO-d_6, δ): 0.97 (3H, d, J=6.8Hz), 1.08 (3H, d, J=5.5Hz), 1.2-3.0 (28H, m), 3.0-4.5 (38H, m), 4.6-5.4

(10H, m), 6.6-7.1 (9H, m), 7.3-7.7 (2H, m), 7.7-8.0 (3H, m), 8.0-8.5 (5H, m), 8.71 (1H, s)

MASS (m/z): 1456 (M^+-1)

Example 22

To a solution of starting compound (22) (0.22 g) in a mixture of methanol (4 ml) and THF (1 ml) were successively added triphenylphosphine (14 mg), tetrakis(triphenylphosphine)palladium(0) (8 mg) and morpholine (40 µl) with stirring and the mixture was stirred at ambient temperature for 3 hours. The reaction mixture was concentrated in vacuo. The resulting residue was dissolved in a mixture of pH 6.86 standard buffer solution and 1N sodium hydroxide, insoluble materials were filtered off and the solution was subjected to column chromatography on ODS (Daiso-gel, SP-120-40/60-ODS-B (Trademark: prepared by Daiso Co., Ltd.)) (100 ml) eluting with 30% acetonitrile in water. The fractions containing the object compound were collected and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give object compound (22) (85 mg).

IR (KBr): 1633, 1537, 1516, 1450, 1234 cm^{-1}

NMR (DMSO-d_6 + D_2O, δ): 0.98 (3H, d, J=7.09Hz), 1.05 (3H, d, J=7.00Hz), 1.15 (6H, d, J=6.21Hz), 1.60-2.30 (8H, m), 2.75-3.45 (14H, m), 3.80-4.50 (10H, m), 4.81 (1H, br s), 6.65-7.20 (8H, m), 7.50-7.80 (5H, m), 7.94 (2H, d, J=8.49Hz)

ESI MASS (m/z)(Negative): 1416.4 (M^++1)

Elemental Analysis Calcd. for $C_{67}H_{91}N_{11}O_{21}S\cdot 7H_2O$:
C 52.10, H 6.85, N 9.97
Found: C 52.29, H 6.60, N 9.61

The following compounds [Examples 23 to 32] were obtained according to a similar manner to that of Example 22.

Example 23

NMR (DMSO-d_6 + D_2O, δ): 0.97 (3H, d, J=6.84Hz), 1.11 (3H, d, J=5.43Hz), 1.30-1.90 (14H, m), 2.80-3.20 (5H, m), 3.22 (3H, s), 3.31 (2H, t, J=6.16Hz), 3.80-4.20 (6H, m), 4.26 (2H, broad s), 4.30-4.50 (3H, m), 4.70-4.90 (1H, m), 6.72 (1H, d, J=8.14Hz), 6.78 (1H, d, J=10.5Hz), 7.01 (1H, s), 7.14 (2H, d, J=8.70Hz), 7.98 (2H, d, J=8.90Hz), 8.05 (2H, d, J=8.68Hz), 8.12 (2H, d, J=8.68Hz)

MASS (m/z)(Negative): 1357.5 (M^+-1)

Example 24

IR (KBr): 2933, 1633, 1531, 1518, 1444, 1419, 1385, 1346 cm^{-1}

NMR (DMSO-d_6, δ): 0.90 (3H, d, J=6.7Hz), 0.98 (3H, d, J=6.7Hz), 1.12 (3H, d, J=5.5Hz), 1.32-2.68 (23H, m), 2.82-2.98 (2H, m), 3.07-4.54 (25H, m), 4.74-5.50 (10H, m), 6.70 (1H, d, J=8.1Hz), 6.78 (1H, d, J=8.1Hz), 7.00 (1H, s), 7.09 (2H, d, J=9.0Hz), 7.36-7.70 (2H, m), 7.86 (2H, d, J=8.8Hz), 8.00-8.50 (6H, m), 8.71 (1H, s), 8.82-8.97 (1H, m)

ESI MASS (m/z): 1407.5 (M^++1)

Elemental Analysis Calcd. for $C_{64}H_{88}N_{12}O_{20}S_2 \cdot 7H_2O$:
C 50.06, H 6.69, N 10.94
Found: C 49.99, H 6.76, N 10.73

Example 25

IR (KBr): 3353.6, 1666.2, 1648.8, 1631.5, 1540.8, 1508.1, 1452.1, 1436.7, 1257.4 cm^{-1}

NMR (DMSO-d_6, δ): 0.98 (3H, d, J=6.7Hz), 1.11 (3H, d, J=5.5Hz), 1.2-5.6 (59H, m), 6.71 (1H, d, J=8.2Hz), 6.78 (1H, d, J=9.6Hz), 7.00 (1H, s), 7.12 (2H, d, J=8.8Hz), 7.44 (1H, d, J=8.5Hz), 7.55 (1H, s), 7.85 (2H, d, J=8.6Hz), 7.99 (2H, d, J=8.5Hz), 8.05 (2H, d, J=8.6Hz), 7.3-8.5 (3H, m), 8.71 (1H, s), 8.7-9.0 (1H, m)

MASS (m/z): 1340.4 (M^--Na)

Elemental Analysis Calcd. for $C_{61}H_{83}N_9O_{23}S \cdot 6H_2O$:
C 50.51, H 6.60, N 8.69
Found: C 50.67, H 6.60, N 8.62

Example 26

IR (KBr): 3380.6, 1675.8, 1648.8, 1621.8, 1540.8, 1506.1, 1454.1, 1434.8, 1257.4 cm^{-1}

NMR (DMSO-d_6, δ): 0.98 (3H, d, J=6.8Hz), 1.03 (6H, d, J=6.3Hz), 1.12 (3H, d, J=5.5Hz), 1.2-5.6 (64H, m), 6.71 (1H, d, J=8.1Hz), 6.77 (1H, d, J=9.4Hz), 7.00 (1H, s), 7.12 (2H, d, J=8.9Hz), 7.43 (1H, d, J=7.7Hz), 7.55 (1H, s), 7.85 (2H, d, J=8.6Hz), 7.99 (2H, d, J=8.8Hz), 8.05 (2H, d, J=8.8Hz), 7.3-8.5 (3H, m), 8.71 (1H, s), 8.82 (1H, d, J=5.7Hz)

MASS (m/z): 1437.4 (M^--1)

Elemental Analysis Calcd. for $C_{67}H_{94}N_{10}O_{23}S \cdot 6H_2O$:
C 52.00, H 6.90, N 9.05
Found: C 51.91, H 6.91, N 8.77

Example 27

IR (KBr): 2931, 2854, 1632, 1510, 1446, 1385, 1325 cm^{-1}

NMR (DMSO-d_6, δ): 0.97 (3H, d, J=6.7Hz), 1.12 (3H, d, J=5.5Hz), 1.08-2.62 (23H, m), 2.62-4.50 (37H, m), 4.66-5.45 (10H, m), 6.70 (1H, d, J=8.1Hz), 6.78 (1H, d, J=8.1Hz), 6.83-7.09 (7H, m), 7.34-8.00 (3H, m), 7.80 (2H, d, J=8.7Hz), 8.00-8.49 (2H, m), 8.71 (1H, s)

MASS (m/z): 1408.4 (M^++1)

Elemental Analysis Calcd. for $C_{66}H_{95}N_{11}O_{21}S \cdot 7H_2O$:
C 51.59, H 7.15, N 10.03
Found: C 51.77, H 7.05, N 9.82

Example 28

IR (KBr): 2974, 2937, 1633, 1533, 1512, 1444, 1383, 1327 cm^{-1}

NMR (DMSO-d_6, δ): 0.98 (3H, d, J=6.7Hz), 1.11 (3H, d,

J=5.2Hz), 1.18 (6H, d, J=6.1Hz), 1.59-2.65 (11H, m), 2.65-4.56 (27H, m), 4.70-5.36 (10H, m), 6.71 (1H, d, J=8.1Hz), 6.78 (1H, d, J=8.1Hz), 7.00 (1H, s), 7.08 (2H, d, J=8.8Hz), 7.38-7.99 (3H, m), 7.68 (2H, d, J=8.7Hz), 7.86 (2H, d, J=8.5Hz), 8.00-8.46 (7H, m), 8.71 (1H, s), 8.80-8.95 (1H, m)

MASS (m/z): 1440.3 (M^++Na)

Elemental Analysis Calcd. for $C_{65}H_{85}N_{11}O_{21}S_2 \cdot 8H_2O$:
C 49.96, H 6.39, N 9.86
Found: C 50.03, H 6.17, N 9.47

Example 29

IR (KBr): 3386.4, 1633.4, 1502.3, 1446.4, 1232.3 cm^{-1}

NMR (DMSO-d_6, δ): 0.96 (3H, d, J=6.6Hz), 1.0-1.3 (9H, m), 1.3-5.6 (57H, m), 6.70 (1H, d, J=8.1Hz), 6.77 (1H, d, J=9.7Hz), 6.9-7.2 (7H, m), 7.3-9.0 (13H, m)

MASS (m/z): 1416.4 (M^--Na)

Example 30

IR (KBr): 3365.2, 1631.5, 1517.7, 1465.6, 1444.4, 1257.4 cm^{-1}

MASS (m/z): 1368.3 (M^--1)

Elemental Analysis Calcd. for $C_{60}H_{79}N_{11}O_{22}S_2 \cdot 7H_2O$:
C 48.15, H 6.26, N 10.30
Found: C 48.26, H 6.17, N 10.35

Example 31

IR (KBr): 3458, 3425, 3398, 3386, 3363, 2935, 1635, 1523, 1462, 1244 cm^{-1}

NMR (DMSO-d_6, δ): 0.98 (3H, d, J=6.7Hz), 1.12 (3H, d, J=5.6Hz), 1.20-1.60 (12H, m), 1.70-2.45 (12H, m), 2.80-3.20 (9H, m), 3.21 (3H, s), 3.40-4.60 (24H, m), 4.70-5.40 (12H, m), 6.71 (1H, d, J=8.1Hz), 6.60-6.80 (1H, m), 7.00 (1H, d, J=1.4Hz), 7.08 (2H, d, J=9Hz), 7.35-7.65 (2H, m), 7.75 (2H, d, J=8.8Hz), 7.80-8.10 (5H,

m), 8.20-8.40 (1H, m), 8.60-8.80 (2H, m), 8.80 (1H, s)
MASS (m/z)(API-ES-Negative): 1497 (M^+-1+Na)
Elemental Analysis Calcd. for $C_{67}H_{91}N_{12}O_{21}S_3 \cdot 8\text{-}1/2H_2O$:
C 48.75, M 6.55, N 10.18
Found: C 48.52, H 6.47, N 9.74

Example 32

IR (KBr): 3464, 3425, 3398, 3386, 3363, 2940, 1635, 1523, 1461 cm^{-1}
NMR (DMSO-d_6, δ): 0.97 (3H, d, J=6.8Hz), 1.12 (3H, d, J=5.6Hz), 1.40-1.60 (6H, m), 1.65-2.45 (9H, m), 2.60-3.20 (6H, m), 3.21 (3H, s), 3.40-3.80 (15H, m), 3.80-4.60 (14H, m), 4.65-5.50 (9H, m), 6.71 (1H, d, J=8.1Hz), 6.75 (1H, dd, J=1.6 and 8.3Hz), 7.03 (1H, d, J=1.6Hz), 7.09 (2H, d, J=9Hz), 7.40-7.65 (2H, m), 7.75 (2H, d, J=8.8Hz), 7.80-8.00 (4H, m), 8.18-8.30 (1H, m), 8.55-8.70 (1H, m), 8.75 (2H, d, J=8.7Hz)
MASS (m/z)(API-ES-Negative): 1453 (M^+)
Elemental Analysis Calcd. for $C_{65}H_{88}N_{12}O_{22}S_2 \cdot 6H_2O$:
C 49.27, H 6.25, N 10.61
Found: C 49.03, H 6.33, N 10.30

Example 33

To a solution of starting compound (33) (12.50 g) and diisopropylethylamine (3.67 ml) in N,N-dimethylformamide (250 ml) was added 4-[2-[4-(4-methoxybutoxy)phenyl]imidazo-[2,1-b][1,3,4]thiadiazol-6-yl]benzoic acid benzotriazol-1-yl ester at room temperature. The solution was stirred for 4 hours at the same temperature, during which period additional 4-[2-[4-(4-methoxybutoxy)phenyl]imidazo[2,1-b][1,3,4]-thiadiazol-6-yl]benzoic acid benzotriazol-1-yl ester was added to the mixture. The reaction mixture was then filtered. To the filtrate was added piperidine (9.33 ml) at room temperature. The solution was stirred for 1 hour at the same temperature. Ethyl acetate was added to the reaction mixture. The powder was

collected by filtration to give crude material (16.12 g). The crude material was purified by column chromatography on ODS to give object compound (33) (11.10 g).

IR (KBr): 1659, 1633, 1529, 1518, 1466, 1444, 1255 cm^{-1}

NMR (DMSO-d_6, δ): 0.98 (3H, d, J=6.7Hz), 1.00 (3H, d, J=5.8Hz), 1.5-2.6 (12H, m), 2.8-3.6 (33H, m), 4.7-5.4 (10H, m), 6.65-6.85 (2H, m), 7.00 (1H, s), 7.15 (2H, d, J=8.9Hz), 7.3-7.7 (2H, m), 7.90 (2H, d, J=8.8Hz), 7.96 (4H, s), 8.0-8.5 (2H, m), 8.71 (1H, s), 8.85 (1H, s)

MASS (m/z): 1392 (M^++23)

Elemental Analysis Calcd. for $C_{60}H_{79}N_{11}O_{22}S_2 \cdot 5H_2O$:
C 49.34, H 6.14, N 10.55
Found: C 49.30, H 6.23, N 10.53

The following compounds [Examples 34 and 44] were obtained according to a similar manner to that of Example 33.

Example 34

IR (KBr): 3463, 3423, 3359, 2941, 2883, 1633, 1614, 1523, 1462 cm^{-1}

NMR (DMSO-d_6, δ): 0.98 (3H, d, J=6.7Hz), 1.10 (3H, d, J=5.6Hz), 1.35-2.20 (10H, m), 2.80-3.20 (2H, m), 3.22 (3H, s), 3.30-3.80 (10H, m), 3.80-4.60 (10H, m), 4.70-5.35 (9H, m), 6.71 (1H, d, J=8.1Hz), 6.65-6.90 (1H, m), 7.00 (1H, br s), 7.09 (2H, d, J=9Hz), 7.40-7.70 (2H, m), 7.43 (2H, d, J=8.6Hz), 7.80-8.00 (4H, m), 8.10-8.50 (2H, m), 8.60-8.80 (3H, m)

MASS (m/z)(API-ES-Negative): 1440 (M^+-1)

Elemental Analysis Calcd. for $C_{64}H_{86}N_{12}O_{22}S_2 \cdot 6\text{-}1/2H_2O$:
C 49.36, H 6.36, N 10.80
Found: C 49.20, H 6.50, N 10.66

Example 35

NMR (DMSO-d_6, δ): 0.90 (3H, d, J=6.7Hz), 0.98 (3H, d,

J=6.8Hz), 1.11 (3H, d, J=5.7Hz), 1.43-5.24 (62H, m), 6.69-8.85 (17H, m)

MASS (m/z): 1408.5

Example 36

MASS (m/z): 1491.4 (M^+-$HN^+Et(iPr)_2$)

Example 37

MASS (m/z): 1576.5 (M^+-$HN^+Et(iPr)_2$)

Example 38

MASS (m/z): 1584.4 (M^+-$HN^+Et(iPr)_2$)

Example 39

The object compound (39) was used directly in the next reaction without purification.

Example 40

The object compound (40) was used directly in the next reaction without purification.

Example 41

The object compound (41) was used directly in the next reaction without purification.

Example 42

The object compound (42) was used directly in the next reaction without purification.

The following compounds [Examples 43 and 44] were obtained according to a similar manner to that of Example 20.

Example 43

NMR (DMSO-d_6 + D_2O, δ): 0.89 (3H, d, J=6.22Hz), 1.14 (3H, br s), 1.35-2.40 (6H, m), 2.65-3.00 (1H, m),

3.60-4.50 (14H, m), 4.55-4.80 (2H, m), 5.28 (1H, s), 6.65-6.80 (2H, m), 6.98 (1H, s), 7.20-7.50 (4H, m), 7.69 (2H, d, J=7.08Hz), 7.84 (2H, d, J=7.27Hz)

ESI MASS (m/z)(Negative): 1185.4 (M^+-1)

Example 44

NMR (DMSO-d_6 + D_2O, δ): 0.95 (3H, d, J=6.77Hz), 1.12 (3H, d, J=4.94Hz), 1.20-1.75 (4H, m), 1.80-2.50 (4H, m), 2.65-2.90 (1H, m), 3.00-3.40 (4H, m), 3.60-4.05 (6H, m), 4.17 (2H, J=7.17Hz), 4.25-4.90 (7H, m), 5.05-5.35 (2H, m), 5.75-6.10 (1H, m), 6.65-6.85 (2H, m), 6.97 (1H, s)

ESI MASS (m/z)(Positive): 1048.3 (M^+)

Example 45

To a solution of a mixture of starting compound (45) (2.0 g), 1,3-dihydroxyacetone (364 mg) and acetic acid (0.58 ml) in a mixture of methanol (30 ml) and DMF (14 ml) was added sodium cyanoborohydride (258 mg) with stirring at ambient temperature, and the mixture was stirred at the same temperature overnight. To the reaction mixture was added ethyl acetate (200 ml). The resulting precipitates were collected by filtration and dried in vacuo. The precipitates were dissolved in a mixture of pH 6.86 standard buffer solution (100 ml) and acetonitrile (20 ml), and the solution was subjected to column chromatography on ODS (Daiso-gel, SP-120-40/60-ODS-B (Trademark: prepared by Daiso Co., Ltd.)) (200 ml) eluting with 15% acetonitrile in water. The fractions containing the object compound were collected and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give object compound (45) (1.63 g).

NMR (DMSO-d_6 + D_2O, δ): 0.98 (3H, d, J=6.75Hz), 1.08 (3H, d, J=5.69Hz), 1.35 (9H, s), 1.45-2.05 (5H, m), 2.15-2.50 (4H, m), 2.70-3.35 (7H, m), 3.50-4.50 (16H, m), 4.70-4.90 (2H, m), 6.71 (1H, d, J=8.13Hz), 6.78 (1H, d, J=9.91Hz), 7.01 (1H, s)

ESI MASS (m/z)(Positive): 1088.4(M^++Na)

The following compounds [Examples 46 to 52] were obtained according to a similar manner to that of Example 45.

Example 46

IR (KBr): 3353.6, 1635.3, 1444.4, 1257.4, 1085.7, 1047.2 cm^{-1}

NMR (DMSO-d_6, δ): 0.97 (3H, d, J=6.6Hz), 1.14 (3H, d, J=5.4Hz), 1.2-5.6 (61H, m), 6.71 (1H, d, J=8.0Hz), 6.77 (1H, d, J=10.3Hz), 6.96 (1H, s), 7.13 (2H, d, J=8.8Hz), 7.97 (2H, d, J=8.7Hz), 8.08 (4H, s), 7.4-8.9 (6H, m)

MASS (m/z): 1371.4 (M^--1)

Example 47

IR (KBr): 3353.6, 1635.3, 1531.2, 1517.7, 1444.4, 1257.4, 1087.7, 1045.2 cm^{-1}

NMR (DMSO-d_6, δ): 0.97 (3H, d, J=6.7Hz), 1.0-5.6 (64H, m), 6.6-6.8 (2H, m), 6.99 (1H, s), 7.14 (2H, d, J=8.9Hz), 7.97 (2H, d, J=8.8Hz), 8.08 (4H, s), 7.3-9.0 (6H, m)

MASS (m/z): 1371.3 (M^--1)

Elemental Analysis Calcd. for $C_{61}H_{84}N_{10}O_{22}S_2 \cdot 7H_2O$:
C 48.86, H 6.59, N 9.34
Found: C 49.00, H 6.39, N 9.24

Example 48

IR (KBr): 3384.5, 1658.5, 1635.3, 1529.3, 1517.7, 1446.4, 1257.4, 1085.7, 1045.2 cm^{-1}

NMR (DMSO-d_6, δ): 0.97 (3H, d, J=6.7Hz), 1.13 (3H, d, J=5.5Hz), 1.2-5.3 (65H, m), 6.91 (1H, d, J=8.1Hz), 6.77 (1H, d, J=9.9Hz), 6.97 (1H, s), 7.13 (2H, d, J=8.9Hz), 7.97 (2H, d, J=8.8Hz), 8.09 (4H, s), 7.4-8.9 (6H, m)

MASS (m/z): 1431.3 (M^--1)

Elemental Analysis Calcd. for $C_{63}H_{86}N_{10}O_{24}S_2 \cdot 8H_2O$:
C 47.96, H 6.64, N 8.88

Found: C 48.21, H 6.35, N 8.87

Example 49

IR (KBr): 3371.0, 1648.8, 1631.5, 1538.9, 1513.8, 1442.5, 1257.4, 1083.8, 1045.2 cm^{-1}

NMR (DMSO-d_6, δ): 0.97 (3H, d, J=6.7Hz), 1.10 (3H, d, J=5.5Hz), 1.2-5.4 (65H, m), 6.71 (1H, d, J=8.2Hz), 6.77 (1H, d, J=10.2Hz), 6.99 (1H, s), 7.14 (2H, d, J=8.7Hz), 7.97 (2H, d, J=8.7Hz), 8.09 (4H, s), 7.3-9.0 (6H, m)

MASS (m/z): 1401.3 (M^--1)

Elemental Analysis Calcd. for $C_{62}H_{86}N_{10}O_{23}S_2 \cdot 7H_2O$:
C 48.68, H 6.59, N 9.16
Found: C 48.83, H 6.39, N 9.13

Example 50

IR (KBr): 3350, 2933, 2862, 1658.5, 1635, 1516, 1444, 1257, 1084, 1043 cm^{-1}

NMR (DMSO-d_6 + D_2O, δ): 0.98 (3H, d, J=6.7Hz), 1.09 (3H, d, J=5.8Hz), 1.2-4.8 (49H, complex m), 3.21 (3H, s), 3.31 (2H, t, J=6.4Hz), 6.8-6.9 (2H, m), 7.02 (1H, br s), 7.15 (2H, d, J=8.9Hz), 7.98 (2H, d, J=8.9Hz), 8.10 (4H, s)

MASS (m/z): 1485.4 (M^++Na)

Elemental Analysis Calcd. for $C_{64}H_{90}N_{10}O_{25}S_2 \cdot 6H_2O$:
C 48.91, H 6.54, N 8.91
Found: C 49.18, H 6.55, N 8.90

Example 51

NMR (DMSO-d_6, δ): 0.86 (3H, d, J=6.3Hz), 0.98 (3H, d, J=6.8Hz), 1.11 (3H, d, J=5.7Hz), 1.21-5.24 (62H, m), 6.69-8.89 (17H, m)

MASS (m/z): 1408.5, 1407.4 (M^+-1)

Elemental Analysis Calcd. for $C_{64}H_{88}N_{12}O_{20}S_2 \cdot 7H_2O$:
C 50.06, H 6.69, N 10.94
Found: C 49.96, H 6.86, N 10.82

Example 52

IR (KBr): 1633, 1606, 1529, 1518, 1466 cm^{-1}

NMR (DMSO-d_6, δ): 0.96 (3H, d, J=6.7Hz), 1.11 (3H, d, J=5.7Hz), 1.2-2.6 (18H, m), 2.8-4.6 (39H, m), 4.7-5.4 (9H, m), 6.7-6.9 (2H, m), 7.0-7.2 (3H, m), 7.3-7.6 (2H, m), 7.75 (2H, d, J=8.7Hz), 7.7-8.0 (5H, m), 8.2-8.5 (1H, m), 8.6-8.75 (1H, m), 8.80 (1H, s), 8.85 (1H, s)

MASS (m/z): 1481 (M^+-1)

Elemental Analysis Calcd. for $C_{66}H_{90}N_{12}O_{23}S_2 \cdot 7H_2O$:
C 49.25, H 6.51, N 10.44
Found: C 49.30, H 6.34, N 10.40

The following compound was obtained according to a similar manner to that of Example 1.

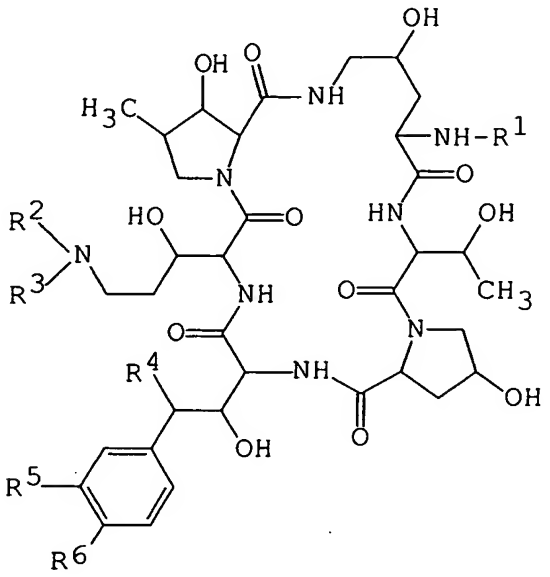
Example 53

IR (KBr): 2937.1, 1651, 1631.5, 1539, 1523.5 cm^{-1}

MASS (m/z): 1293.3 (M^++1)

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A polypeptide compound of the following general formula (I):



(I)

wherein

R^1 is hydrogen or acyl group,

R^2 is hydrogen or acyl group,

R^3 is lower alkyl which has one or more hydroxy or protected hydroxy,

R^4 is hydrogen or hydroxy,

R^5 is hydrogen, hydroxy, lower alkoxy or hydroxysulfonyloxy, and

R^6 is hydroxy or acyloxy,

or a salt thereof.

2. A compound of claim 1, wherein

R^1 is hydrogen or acyl group,

R^2 is hydrogen,

R^3 is lower alkyl which has one or more hydroxy,

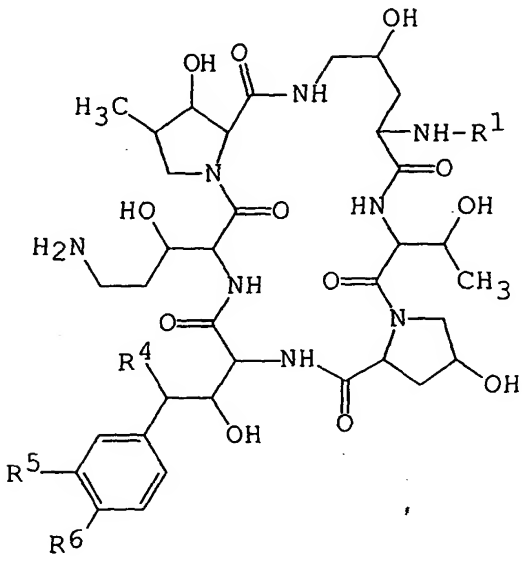
R^4 is hydrogen or hydroxy,

R^5 is hydroxysulfonyloxy and

R^6 is hydroxy.

3. A process for preparing a polypeptide compound (I) of claim 1, or a salt thereof,
which comprises,

1) reacting a compound (II) of the formula:

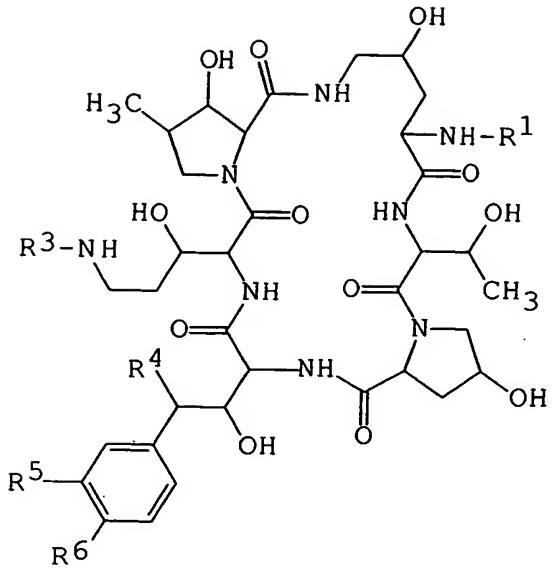


(II)

wherein R^1, R^4, R^5 and R^6 are defined in claim 1,
or its reactive derivative at the amino group or a salt thereof, with a compound (III) of the formula:

$$R^3{=}O \qquad \text{(III)}$$

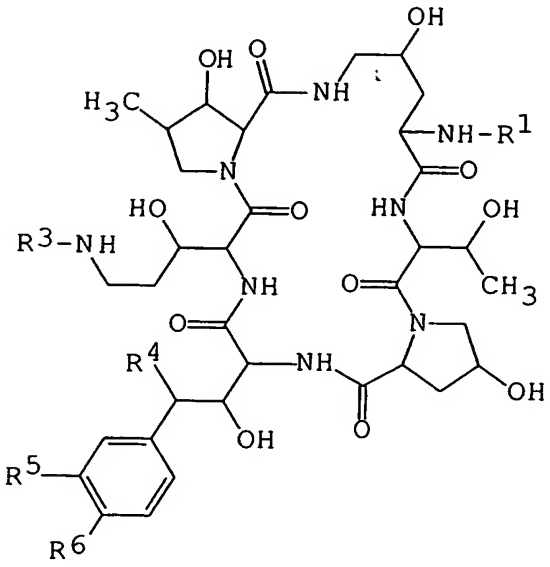
wherein R^3 is defined in claim 1,
or its reactive derivative or a salt thereof, to give a compound (Ia) of the formula:



(Ia)

wherein R^1, R^3, R^4, R^5 and R^6 are defined above, or a salt thereof, or

ii) reacting a compound (Ia) of the formula:

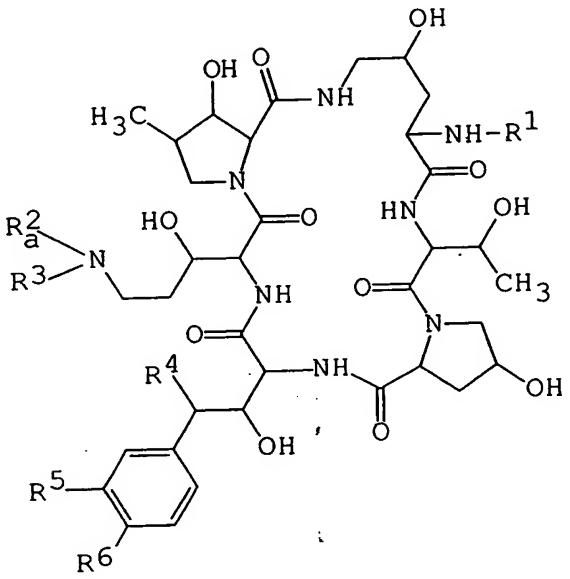


(Ia)

wherein R^1, R^3, R^4, R^5 and R^6 are defined in claim 1, or its reactive derivative at the amino group or a salt thereof, with a compound (IV) of the formula:

$$R_a^2\text{-OH} \qquad \text{(IV)}$$

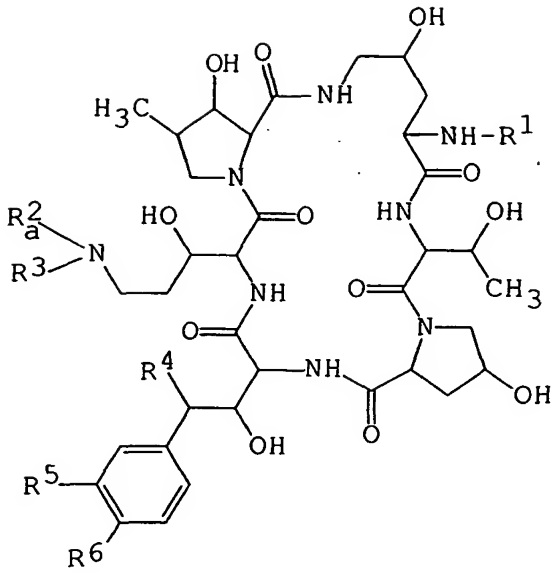
wherein R_a^2 is acyl group,
or its reactive derivative at the carboxy group or a salt thereof, to give a compound (Ib) of the formula:



(Ib)

wherein R^1, R_a^2, R^3, R^4, R^5 and R^6 are defined above, or a salt thereof, or

iii) subjecting a compound (Ib) of the formula:

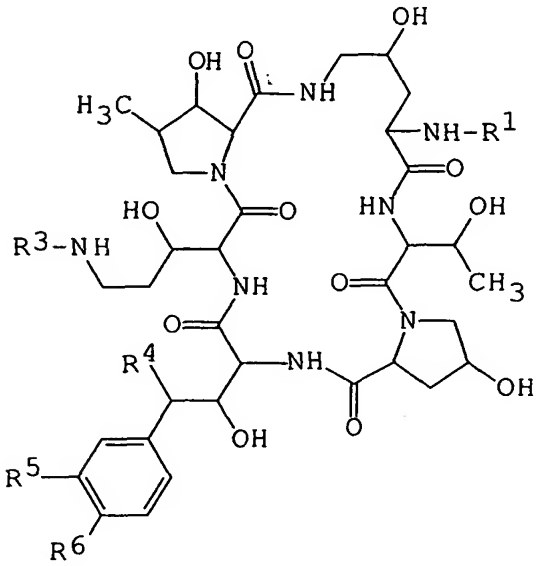


(Ib)

wherein R^1, R^3, R^4, R^5 and R^6 are defined in claim 1,

R^2_a is acyl group,

or a salt thereof, to elimination reaction of the acyl group, to give a compound (Ia) of the formula:

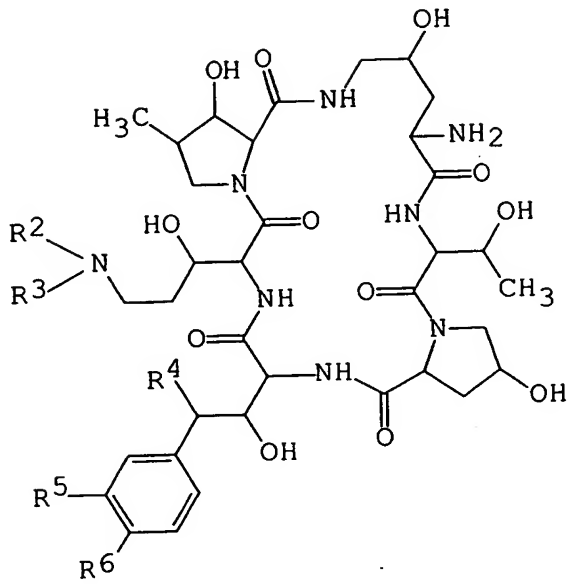


(Ia)

wherein R^1, R^3, R^4, R^5 and R^6 are defined above,

or a salt thereof, or

iv) reacting a compound (Ic) of the formula:

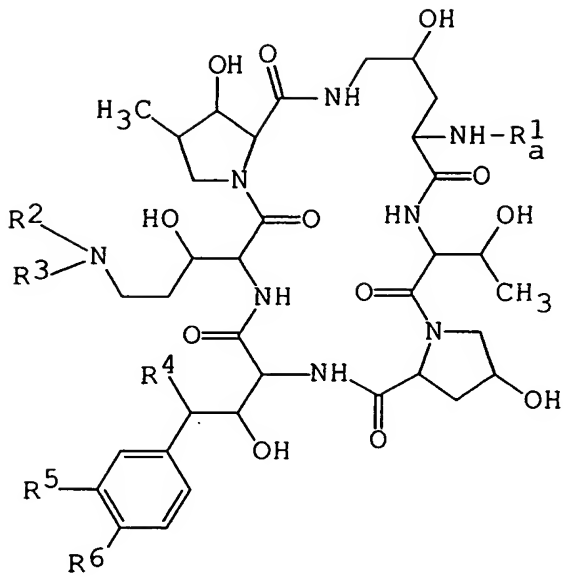


(Ic)

wherein R^2, R^3, R^4, R^5 and R^6 are defined in claim 1, or its reactive derivative at the amino group or a salt thereof, with a compound (V) of the formula:

$$R^1_a\text{-OH} \qquad \text{(V)}$$

wherein R^1_a is acyl group,
or its reactive derivative at the carboxy group or a salt thereof, to give a compound (Id) of the formula:



(Id)

wherein R^2, R^3, R^4, R^5 and R^6 are defined in claim 1,
R^1_a is defined above,
or a salt thereof.

4. A pharmaceutical composition which comprises, as an active ingredient, a compound of Claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carrier or excipients.

5. Use of a compound of Claim 1 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament.

6. A compound of Claim 1 or a pharmaceutically acceptable salt thereof for use as a medicament.

7. A method for the prophylactic and/or therapeutic treatment of infectious diseases caused by pathogenic microorganisms, which comprises administering a compound of claim 1 or a pharmaceutically acceptable salt thereof to a human being or an animal.

8. A commercial package comprising the pharmaceutical composition of claim 4 and a written matter associated therewith, wherein the written matter states that the pharmaceutical composition can or should be used for preventing or treating infectious disease.

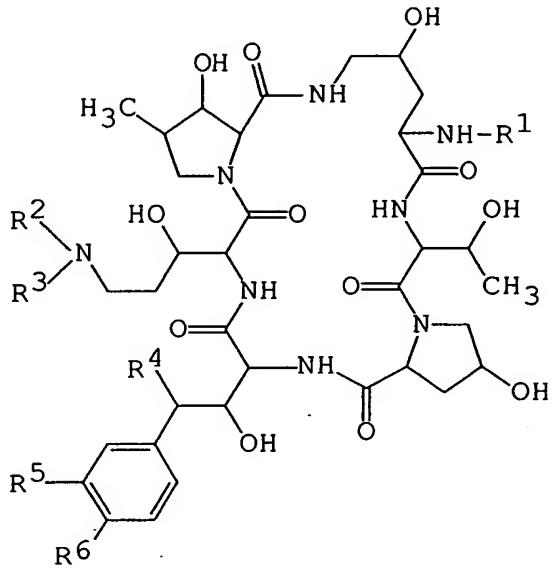
DATED this 21st day of August 2000

Fujisawa Pharmaceutical Co., Ltd

By DAVIES COLLISON CAVE
Patent Attorneys for the Applicant

A B S T R A C T

This invention relates to new polypeptide compound represented by the following general formula (I):



(I)

wherein
R^1, R^2, R^3, R^4, R^5 and R^6 are as defined in the description or a salt thereof which has antimicrobial activities (especially, antifungal activities), inhibitory activity on b-1,3-glucan synthase, to process for preparation thereof, to a pharmaceutical composition comprising the same, and to a method for prophylactic and/or therapeutic treatment of infectious diseases including Pneumocystis carinii infection (e.g. Pneumocystis carinii pneumonia) in a human being or an animal.